NAMRL MONOGRAPH 34

BIOMEDICAL EFFECTS OF CHEMICAL-THREAT-AGENT ANTIDOTE AND PRETREATMENT DRUGS: AN ABSTRACTED BIBLIOGRAPHY

VOLUME I

J. M. Lentz, G. G. Reams, and C. A. DeJohn

April 1986

NAVAL AEROSPACE MEDICAL RESEARCH LABORATORY

PENSACOLA, FLORIDA

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Naval Medical Research and Development Command
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PROLOGUE

The Naval Aerospace Medical Research Laboratory (NAMRL) is engaged in a research effort to determine the effects on performance of chemical warfare antidotes. This monograph is part of a continuing literature review of antidote agents and related pretreatment medications. The monograph is intended to be the first of several volumes that will form the basis for a comprehensive review paper.

We have chosen a printing format, tear-out 5 x 8 index cards, to reflect our emphasis on producing a versatile working document, which can be supplemented with future abstracts. A topic area index is provided at the end of the monograph. The topic area descriptions for each abstract can be found at the bottom of each 5 x 8 card and represent three general areas: drug (e.g., atropine, oxime, pyridostigmine, nerve agent, drug - other); biomedical discipline (e.g., vision, auditory, spatial, cardiopulmonary, musculoskeletal, performance, pharmacology, cutaneous, cortical, review); and application (e.g., human, non-human).

A numerical filing system can be found at the top right side of each 5 x 8 card. The numerical system corresponds to an alphabetical order by author. This initial volume uses numerical intervals of ten, which will allow abstracts from future volumes to be merged and still retain a numerical and alphabetical order. Only English language articles or those with an English-language summary are included.

Each abstract contains the following sections of information: Authors, Title, Reference, Drugs (including dosages), Subjects (number and type), Procedures (brief general description), Findings (brief listings of major findings using the author's direct quotes where possible), Comment (comments by the authors of this bibliography; this section is sometimes omitted), and Index (the topic area index is described in the preceding paragraphs). In some cases, it was necessary to use more than one 5 x 8 card to adequately abstract the article. In cases where two cards are used, the reader may want to staple or affix the second card to the first card.

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The bibliographic abstracts in this report are part of a project to assess biomedical effects of chemical warfare antidote agents and related pretreatment drugs. Specific attention has been focused on the biomedical effects in the following general areas: vision, auditory, spatial orientation, musculoskeletal, cardiopulmonary, cognitive performance, pharmacology, cutaneous stimuli, and cortical effects. In some cases, the bibliography addresses other therapeutic drugs that may be used simultaneously with chemical warfare antidotes.

AUTHORS: Adams, R., Venna, P., Jackson, A., and Miller, R.

TITLE: Plasma pharmacokinetics of intravenously administered atropine in normal human subjects

REFERENCE: Journal of Clinical Pharmacology, 1982, 22, 477-481.

DRUGS: Atropine (1 mg i.v.)

SUBJECTS: 6 humans

PROCEDURES: A single 1-mg i.v. bolus of atropine was administered. Atropine plasma levels were then collected for 24 h and analyzed by radioimmunoassay.

FINDINGS:
1. The mean biologic half life was 4.125 h. Earlier studies, based on non-specific assays reported values of 1.3 to 2.1 h.
2. Maximum change in pulse rate occurred between 12 to 16 min. The effect was observed for 6 h; at which time rates were still greater than preinjection rates. A statistically significant correlation existed between average pulse rates and average atropine tissue levels. No correlation existed between pulse rate and plasma levels of atropine.

(Cont'd) 10

3. There was no significant change in blood pressure.
4. Atropine was widely distributed in tissues. Atropine disappears rapidly from the plasma after i.v. administration.

INDEX: Atropine, Pharmacology, Human

AUTHORS: Ainslie, E. H., deCandole, C. A., Hardman, A. C., and Richardson, B. A.

TITLE: Response of the circulation to passive postural change after atropine and metaraminol

REFERENCE: Canadian Medical Association Journal, 1962, 86, 110-112.

DRUGS: Atropine (2 mg)

SUBJECTS: 56 humans

PROCEDURES: Half of the subjects were given 2 mg atropine alone, half given atropine and metarminol. Subjects were then run through tilt-table experiments and measurements of blood pressure and heart rate were recorded over the next 38 minutes.

FINDINGS:
1. In the horizontal position with atropine, heart rate, systolic and diastolic pressures were higher than baseline.
2. In the vertical position with atropine, heart rate increased to same number of beats as controls, but at a slower rate. Systolic and diastolic pressures fell to a lower level than controls.

(Cont'd) 20

3. In the horizontal position with atropine and metarminol, heart rates were the same as atropine alone. Systolic and diastolic pressures were higher than with atropine alone.
4. In the vertical position with atropine and metarminol, heart rate increased by the same amount as with controls and atropine alone. Systolic and diastolic pressures fell further than atropine alone, but remained at higher overall levels.

COMMENT: Other studies have suggested fainting was likely to occur after atropine administration. This was not found in this study.

INDEX: Atropine, Drug (Other), Cardiopulmonary, Human

30

AUTHORS: Albanus, G. L.

TITLE: An oxime of atropine - some pharmacological observations

REFERENCE: Biochemical Pharmacology, 1963, 12, 218-219.

DRUGS: PGTO (Phenylglyoxylic Acid Tropylester Oxime)

SUBJECTS: Cats - 5 mg kg body wt
Rat muscle preparations - $5x10^{-5}M$, $5x10^{-6}M$
Mice - 25-37 mg/kg body wt

PROCEDURES: Muscle preparations, live studies to determine restoration of autonomic function as well as reactivation of acetylcholine.

FINDINGS:
1. Quite toxic.
2. Less effective in restoring autonomic function than atropine.
3. Less effective than other oximes in reactivation of enzymes.

INDEX: Oxime, Atropine, Pharmacology, Non-Human

40

AUTHORS: Antonelli, A. R., and Calearo, C.

TITLE: Drug effects on the auditory speech discrimination mechanism: The action of atropine and scopolamine

REFERENCE: Acta Otolaryngologica (Stockh), 1964, 58, 105-110.

DRUGS: Atropine 10 mg p.o. and 4-5 mg s.q.
Scopolamine 4 mg p.o. and 1 mg s.q.

SUBJECTS: 12 humans

PROCEDURES: As soon as the drugs induced clear-cut autonomic changes (pulse, blood pressure, salivation, pupillary diameter, and accommodation), audiometery was started. Audiometry included normal, interruption, distorted and compressed intelligibility, pure tone threshold, and inhibition of contralateral tonal adaptation.

FINDINGS: The impairment of performance on tests with low redundancy material is particularly evident for the interrupted and distorted speech and only slight for compressed speech. Scopolamine and atropine do not alter the receptive phase of the auditory-integration of speech material. They do not influence the transmission of impulses along the auditory pathways. Pure tone tests and intelligibility of normal speech are not affected. The point of

attack of the drugs appears to be in the perceptive phase, where patterns are decoded and their significance is drawn through comparison with previously memorized models.

INDEX: Atropine, Drug (Other), Auditory, Human

50

AUTHORS: Arena, J. M.

TITLE: Atropine Poisoning: A report of two cases from Jimson Weed

REFERENCE: Clinical Pediatrics, 1963, 2, 182-184.

DRUGS: Atropine - raw, naturally occurring alkaloid

SUBJECTS: Humans - 2 young males

PROCEDURES: Accidental ingestion of Jimson Weed

FINDINGS: Young children are perhaps more susceptible to poisoning. High temperatures, dry mouth, dilated pupils, flushed skin, and excitability were reported.

COMMENT: An observation of signs and symptoms of atropine intoxication in children.

INDEX: Atropine, Pharmacology, Human

AUTHORS: Baker, R., Adams, A., Jampolsky, A., Brown, B., Hagerstrom-Portnoy, G., and Jones, R.

TITLE: Effects of atropine on visual performance

REFERENCE: Military Medicine, 1983, 148, 530-535.

DRUGS: Atropine (2 mg/70 kg of body weight, i.m.)

SUBJECTS: EXPERIMENT ONE: 10 humans
EXPERIMENT TWO: 6 humans

PROCEDURES: EXPERIMENT ONE. A vision test battery was administered and pulse and blood pressure were taken before injection and 30, 120, and 240 min after injection. EXPERIMENT TWO: Subjects repeatedly focused targets at two distances, and target identification reaction times were measured. A second task required a visual search for a random target, while suppressing vestibular eye movements induced by rotation.

FINDINGS: EXPERIMENT ONE
1. Atropine reduced lens accommodation 16%.
2. Pupil area increased by 50%.
3. Contrast sensitivity decreased slightly at all frequencies 4 h after injection.

(Cont'd) 60

4. Accommodative and pupil dynamics, visual acuity, intraocular pressure, saccadic eye movements, depth perception, and color vision were not significantly affected.

EXPERIMENT TWO
1. Atropine had no effect on either task.

INDEX: Atropine, Vision, Spatial, Human

70

AUTHORS: Barkman, R., Edgren, B., and Sundwall, A.

TITLE: Self-administration of pralidoxime in nerve gas poisoning with a note on the stability of the drug

REFERENCE: Journal of Pharmacy and Pharmacology, 1963, 15, 671-677.

DRUGS: Pralidoxime methane sulphonate (10 or 20 mg/kg i.m.)

SUBJECTS: 24 humans

PROCEDURES: Blood samples

FINDINGS: 10 mg/kg produced (4 μg/ml) within 6 min maintained for 90 min
20 mg/kg produced (4 μg/ml) maintained for 170 min
"Except for pain at the site of injection, which disappeared after a few h, no serious side reactions could be detected." 1/3 Ss had drowsiness, 1 S diplopia. "Special attention was therefore paid to the possibility of necroses at the site of injection but no signs could be detected." "The drug can be stored for 5 years at 5° with less than 7 percent decomposition."

INDEX: Oxime, Pharmacology, Human

80

AUTHORS: Beerman, B., Hellstrom, K., and Rosen, A.

TITLE: The gastrointestinal absorption of atropine in man

REFERENCE: Clinical Science, 1971, 40, 95-106.

DRUGS: (a) Atropine (2 mg) - orally
(b) Same as above but infused in distal jejunum

SUBJECTS: 10 humans

PROCEDURES: Labeled atropine, gastric and intestinal samples, venous blood, urine, feces

FINDINGS:
- "... 90% of the given label is absorbed in the proximal part of the small intestine."
- maximum recovery - 3% plasma, 65% urine, 5% feces
- "...substantial absorption occurs distal to [the jejunum]"
- plasma maximum level = approx. 3% of oral dose, peak reached at 1 h
- "The uptake of orally administered radioactivity occurred mainly in the duodenum and in the jejunum whereas none took place in the stomach."

(Cont'd) 80

- "The present study demonstrates that atropine is suitable for oral administration as evidenced by the complete absorption and the small individual variations in this respect."

INDEX: Atropine, Pharmacology, Human

90

AUTHORS: Berghem, L., Bergman, U., Schildt, B., and Sorbo, B.

TITLE: Plasma atropine concentrations determined by radioimmunossay after single-dose i.v. and i.m. administration

REFERENCE: British Journal of Anaesthesia, 1980, 52, 597.

DRUGS: Atropine, 1 mg i.v. and i.m.

SUBJECTS: 10 humans

PROCEDURES: Pre-anesthetic atropine given at doses of 1 mg i.m. or i.v. was measured at intervals using RIA techniques.

FINDINGS: Plasma levels of atropine 10 min after i.v. administration were less than 5% of administered dose. I.M. atropine reached peak plasma levels within 30 min and decreased slowly. One h after administration, plasma concentrations were the same, whether given i.v. or i.m.

(Cont'd) 90

COMMENT: Other authors suggest a decrease in plasma atropine followed by a transient increase when given i.v. This was not observed in this study. RIA method discussed by others as sensitive and specific.

INDEX: Atropine, Pharmacology, Human

100

AUTHORS: Bergman, K. R., Pearson, C., Waltz, G. W., and Evan, R., III

TITLE: Atropine-induced psychosis

REFERENCE: Chest, 1980, 78, 891-893.

DRUGS: Nebulized atropine 1.2 mg with terbulaline 2.0 mg.; reversed with physostigmine 1.0 mg i.v.

SUBJECTS: 59-year-old white male

PROCEDURES: Case history

FINDINGS: Patient became psychotic, manifested pressured speech, flight of ideas, visual hallucinations, emotion lability, and ambivalence.

INDEX: Atropine, Pharmacology, Human

AUTHORS: Bergmann, F., Chaimovity, M., and Pasternak, V.

TITLE: The influence of atropine and eserine on central nystagmus: A contribution to the pharmacology of optic nystagmus

REFERENCE: Neuropharmacology, 1975, 14, 193-200.

DRUGS: Atropine (0.1 - 1.0 mg/kg), Eserine (100 μg/kg)

SUBJECTS: 40 rabbits

PROCEDURES: Electrical stimulation of optic pathway resulting in "central nystagmus".

FINDINGS:
1. Atropine inhibited the nystagmic response (duration and number of beats) (dose related).
2. Eserine produced biphasic response - enhancement then inhibition.
3. "Quaternary atropine methyl nitrate reduced nystagmus in a manner similar to the effect of atropine [atropine sulphate],...."
4. "Small doses of atropine, injected before eserine suppressed the enhancement phase but strengthened the inhibitory effect;...Probably two different cholinergic elements are involved...."

(Cont'd) 110

5. Atropine peak effect approximately 90 min after i.v. infusion.

INDEX: Atropine, Drug (Other), Spatial, Non-Human

AUTHORS: Bertram, U., Kasten, A., Lullmann, H., and Ziegler, A.

TITLE: Improved treatment of organophosphate intoxication by use of scopolamine or dexetimide

REFERENCE: Experientia, 1977, 33, 1196-1197.

DRUGS: (All doses in μmoles/kg body weight)
Atropine (10-20), scopolamine (10-20), dexetimide (10-20), obidoxime (10-100)

SUBJECTS: Mice (N not given), rabbits (N=82)

PROCEDURES: LD_{50}

FINDINGS:
- "The combined prophylactic treatment by atropine plus obidoxime resulted in a protection factor of 28 which is in accordance with other reports. An increase of the atropine dosage did not yield higher protection. Replacing atropine by the stronger centrally acting drugs scopolamine or dexetimide proved to result in far superior protection, as demonstrated by the protective factors of 183 and 180, respectively."

(Cont'd) 120

- "The results of our animal experiments demonstrate that the combination of dexetimide and obidoxime is superior to the combination of atropine and obidoxime recommended for the therapy of organophosphate intoxication in man. In consequence of the results reported here we suggest the use of dexetimide or scopolamine in the treatment of organophosphate intoxication to improve the rate of recovery."
- The authors suggest that the unsuccessful treatment with atropine or atropine plus oximes is partially the result of atropine's relative inability to work on CNS — the blood-brain barrier is more readily crossed by cholinolytic drugs like dexetimide (and scopolamine).
- organophosphate - D.F.P., paraoyone, OMPA.

INDEX: Atropine, Drug (Other), Pharmacology, Non-Human

AUTHORS: Boren, J. J., and NaVarro, A. P.

TITLE: The action of atropine, benactyzine and scopolamine upon fixed interval and fixed ratio oehavior

REFERENCE: Journal of Experimental Analysis of Behavior, 1959, 2, 107-115.

DRUGS: Atropine, benoctyzine, scopolamine - varying doses

SUBJECTS: 2 rats

PROCEDURES: Water deprived rats were trained on a a fixed ratio/fixed interval schedule across each drug at various doses.

FINDINGS:
1. At higher doses, temporal patterns were disrupted and changed to steady responding.
2. At medium doses, the fixed interval or time sequence was disrupted, but number of responses was not.
3. At low doses, there was no change in temporal patterning, but evidence of stimulation of number of responses and times.

(Cont'd) 130

COMMENT: Suggests central effect altering time interval and ratio patterns.

INDEX: Atropine, Drug (Other), Performance, Non-Human

AUTHORS: Bradley, P. B.

TITLE: The effect of atropine and related drugs on the EEG and behaviour

REFERENCE: Progress in Brain Research, 1968, 28, 3-13.

DRUGS: Atropine, physostigmine (various doses)

SUBJECTS: Cats

PROCEDURES: Review article - EEG & single unit recordings. Some behavioral testing (conditional avoidance and reward).

FINDINGS: "We concluded from the results of these experiments that the presence of the dissociated EEG as produced by administration of atropine did not modify the behavior of the animals within the limits of the methods used...."However, from the results of our experiments it would appear that either the presence of slow waves in the electrocorticogram has no particular relevance for behavior or the cortical mechanisms which are affected by drugs producing dissociation are not those concerned with behavioral responses."

(Cont'd) 140

COMMENT: Atropine produces high-voltage slow waves with spindle activity in wide awake (or excited) animals - normally seen in the quiet drowsy animal.

INDEX: Atropine, Drug (Other), Review, Performance, Non-Human

AUTHORS: Brodeur, J., and Alary, J. G.

TITLE: Potentiation by phenobarbital of the protection afforded by atropine and 2-PAM against parathion poisoning in rats.

REFERENCE: Canadian Journal of Physiology and Pharmacology, 1965, 45, 358-360.

DRUGS: Atropine sulphate (100 mg/ml), phenobarbital sodium (50 mg/ml), 2-PAM (50 mg/ml) all i.p. - dosage amounts varied.

SUBJECTS: 224 rats

PROCEDURES: LD_{50}

FINDINGS: LD_{50}

2.7 mg/kg for Parathion (alone)
6.8 mg/kg following Atropine and 2 PAM
9.7 mg/kg following Phenobarbital
40.0 mg/kg following Atropine + 2 PAM + Phenobarbital

(Cont'd) 150

"These results show that pretreatment of rats with phenobarbital potentiates the protection afforded by atropine and 2-PAM against parathion poisoning."

COMMENT: Phenobarbital is a microsomal enzyme inducer which may cause the liver to detoxify parathion more quickly.

INDEX: Atropine, Oxime, Drug (Other), Pharmacology, Non-Human

AUTHORS: Brown, B., Baker, R., Adams, A., Haegerstrom-Portnoy, G., Jones, R., and Jampolsky, A.

TITLE: Investigation of visual performance after administration of cholinergic blocking agents. II. Atropine

REFERENCE: Report No. 821, 1982, U. S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD 21701 (Optical Sciences Group, Inc., Petaluma, CA 94952).

DRUGS: Atropine (2 mg/70 kg body weight)

SUBJECTS: 2 experiments; 10 humans (20-30 yrs), 6 humans (21-32 yrs)

PROCEDURES: EXPERIMENT 1. Tested accommodation, heterophoria, pupil dynamics, static visual acuity, refractive state, contrast sensitivity, glare recovery, intraocular pressure, depth perception, etc. EXPERIMENT 2. Tested visual search ability.

FINDINGS: Demonstrated long-lasting changes in accommodative function, pupil size, and the contrast sensitivity function, which though relatively small, may affect military taskings. However, second experiment made to mimic real-world task did not confirm this conclusion.

(Cont'd) 160

COMMENT: The second experiment may have used too broad a definition when it said it embodied aspects of real-world performance.

INDEX: Atropine, Vision, Human

AUTHORS: Brown, B., Haegerstrom-Portnoy, G., Adams, A., Jones, R. T., and Jampolsky, A.

TITLE: Investigation of visual performance after administration of cholinergic blocking agents. I. Benactyzine

REFERENCE: Report No. 801, 1980, U. S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD 21701 (Optical Sciences Group, Inc. San Rafael, CA.)

DRUGS: Benactyzine Hydrochloride (4.14 mg/70 kg i.m.)

SUBJECTS: 18 Humans (25-32 yrs)

PROCEDURES: 2 experiments: (1) (6 subjects) 15 min post-injection subject evaluated using vision test battery; 5 min rest, then retested again; rest one hour, then tested a third time; (2) (12 subjects) tested at 15, 90, and 270 min post-injection.

FINDINGS:
1. Reduced static visual acuity by 5% (rapid onset), peaked at 60 min.
2. Dynamic visual acuity is significantly reduced.
3. Amplitude of accommodation is dramatically reduced.

(Cont'd) 170

4. Increase in pupil size.
5. Little or no change in heterophoria (distance or near).
6. Tracking eye movements not affected.
7. Large changes in contrast sensitivity.
8. No change in color vision.
9. Reduction of intraocular pressure.

INDEX: Drug (Other), Vision, Human

AUTHORS: Calesnick, B., Christensen, J. A., and Richter, M.

TITLE: Human toxicity of various oximes

REFERENCE: Archives of Environmental Health, 1967, 15, 599-608.

DRUGS: 2 PAM (1, 2 or 4 g), P_2S (1.25 to 5 g), $TMB4Cl_2$ (12.5 to 33.2 mg/kg).

SUBJECTS: 40 humans

PROCEDURES: The subjects were given either varying single dose of the oximes, p.o., i.m. or i.v., or given the drugs chronically p.o. Various physiologic parameters were monitored.

FINDINGS: 2-PAM and P_2S i.v. produced a primary elevation of systolic and diastolic pressures. No change in heart rate. A secondary hypotensive episode developed 3-4 h later. TMB4 did not have a hypertensive effect but had a hypotensive effect. 2-PAM could be given p.o. (5 g/day) without GI effects as opposed to P_2S and TMB4, which did have GI side effects. TMB4 does show signs of hepatotoxicity.

(Cont'd) 180

COMMENT: 2 PAM has much fewer side effects.

INDEX: Oxime, Pharmacology, Cardiopulmonary, Human

AUTHORS: Cavanaugh, M. J., and Cooper, D. M.

TITLE: Inhaled atropine sulfate dose response characteristics

REFERENCE: American Review of Respiratory Disease, 1976, 114, 517-524.

DRUGS: Atropine (0.005, 0.01, 0.025, 0.05 and 0.10 mg/kg), Isoproteranol (1 mg)

SUBJECTS: 20 humans

PROCEDURES: Testing in a single blind, randomized fashion was carried out with atropine, or isoproteranol, or a combination of 0.1 mg of atropine per kg and 1 mg of isoproteranol. Pulmonary function testing was conducted before nebulization and at regular intervals after treatment.

FINDINGS:
1. A fully effective dose of nebulized atropine sulfate as a bronchodilator is 0.05 to 0.1 mg/kg.

(Cont'd) 190

2. Atropine is as effective a bronchodilator as isoproteranol, has fewer chronotropic side effects, and has a longer duration of action. The combination of isoproteranol with optimal doses of atropine failed to produce bronchodilation greater than that obtainable with atropine alone.
3. The significant increases in $Vmax_{50}$, $Vmax_{75}$, and specific conductance (SG_{aw}) support the hypothesis that atropine acts at sites from small through large airways, although the relatively larger increases in SG_{aw} compared with $Vmax_{50}$ or $Vmax_{75}$ suggests that atropine has proportionately greater activity in larger airways.
4. The observed significant decrease in Rv/TLL suggests that atropine in adequate doses acts on small airways, or perhaps relaxes the chest wall.
5. $Vmax_{50}$ observed/$Vmax_{50}$ predicted is a linear function of $Vmax_{50}$ baseline/$Vmax_{50}$ predicted, demonstrating that the response obtained after inhalation of atropine is determined by both drug dosage and baseline pulmonary function: that is, the efficacy is related to the degree of bronchoconstriction before the use of medication.

INDEX: Atropine, Drug (Other), Cardiopulmonary, Human

AUTHORS: Chamberlain, D. A., Turner, P., and Sneddon, J. M.

TITLE: Effects of atropine on heart rate in healthy man

REFERENCE: Lancet, 1967, 2, 12-15.

DRUGS: Predosed with propranolol (80 mg) - 90 min prior
i.v. atropine sulphate (0.6, 1.2, 1.8, 2.4, 3.0 mg)

SUBJECTS: 10 humans - ages 22-23

PROCEDURES: Heart rate during rest and exercise

FINDINGS:
1. "...atropine always had most influence on the resting heart rate. This was to be expected because one of the principal mechanisms of exercise tachycardia is a withdrawal of vagal inhibition on the sinoatrial node; vagal tone is absent at maximal heart rates which are consequently unaffected by atropine."
2. "The supine resting heart rate increased progressively as greater doses of atropine were given,...."
3. Side effects - "...at the higher dose ranges, some also complained of nausea, lightheadedness, and of difficulty with micturition."

(Cont'd) 200

4. "...at rest the fall in heart rates achieved by propranolol were negatively correlated with subsequent rises after maximal doses of atropine. This implies that people with slow resting heart rates have not only high vagal tone but also little sympathetic tone;...."

COMMENT: Finding #4 suggests that atropine may produce a stronger effect in well conditioned athletes (lower resting heart rate).

INDEX: Atropine, Cardiopulmonary, Human

AUTHORS: Clement, J. G.

TITLE: Pharmacological actions of HS-6, an oxime, on the neuromuscular junction

REFERENCE: European Journal of Pharmacology, 1979, 53, 135-141.

DRUGS: HS-6 (3.9×10^{-3}M to 1.16×10^{-4}M)

SUBJECTS:
(1) Rat diaphragm preparations
(2) Chick biventer cervicis preps
(3) Guinea-pig ileum longitudinal muscle
(4) Bovine erythrocyte AChE ACTW
(5) Bovine erythrocytes

PROCEDURES: The effects of HS-6 on the neuromuscular junction was investigated.

(Cont'd) 210

FINDINGS:
- HS-6 did not cause a contraction in (2) whereas it did in (3).
- HS-6 produced a hemicholinum like neuromuscular blockade in (2) and (5).
- HS-6 inhibited choline uptake in (5).
- HS-6 inhibited the contractions of various nicotine agonists in (2) and augmented ACh contractions.

INDEX: Oxime, Musculoskeletal, Non-Human

AUTHORS: Clement, M. B.

TITLE: Atropine premedication for electric convulsion therapy

REFERENCE: British Medical Journal, 1962, 1, 228-229.

DRUGS: Atropine (1 mg s.q. or i.v.)

SUBJECTS: 200 humans

PROCEDURES: 100 patients were given 1 mg of atropine subcutaneously one half hour before electric convulsion therapy (ECT) and 100 were given 1 mg of atropine i.v. 75 seconds before ECT. Heart rate was monitored by palpitating radial pulse and auscultating the apex beat for 15 s before the shock and 60 s after it.

FINDINGS:
SUBCUTANEOUS ATROPINE - 22 patients had complete disappearance of heart sounds and pulse for 1.5 to 5 s from the beginning of ECT. Eleven patients developed extrasystoles.

INTRAVENOUS ATROPINE - One patient developed severe bradycardia for 5 s. One patient had complete disappearance of heart sounds and pulse for 4 s. Eight patients developed extrasystoles.

(Cont'd) 220

COMMENT: Recommends i.v. rather than s.q. atropine as a pre-medication for ECT.

INDEX: Atropine, Cardiopulmonary, Human

AUTHORS: Craig, F. N.

TITLE: Effects of atropine, work and heat on heart rate and sweat production in man

REFERENCE: Journal of Applied Physiology, 1952, 4, 826-833.

DRUGS: Atropine sulfate (2 mg i.m.)

SUBJECTS: 3 humans

PROCEDURES: Environments (21°C and 60% R.H. or 30°C and 80% R.H.)
Test Situations - (rest or walking on treadmill)
Responses - heart rate, sweat production, body temp, respiratory rate and volume

FINDINGS:
"The intramuscular injection of 2 mg of atropine produced an acceleration of the heart of about 37 beats per minute that was uniform over the whole range of conditions."
"Under conditions of active sweating the greatest effect of 2 mg atropine on sweat production was an inhibition amounting to 48 per cent."

(Cont'd) 230

"The increase in heart rate became well developed within 15 minutes...."
"No clear cut effect of atropine on respiratory rate and minute volume was seen."

INDEX: Atropine, Cardiopulmonary, Human

AUTHORS: Crook, J. W., Goodman, A. I., Colbourn, J. L., Zvirblis, P., Oberst, F. W., and Wills, J. H.

TITLE: Adjunctive value of oral prophylaxis with the oximes 2 PAM lactate and 2 PAM methanesulfonate to therapeutic administration of atropine in dogs poisoned by inhaled savin vapor

REFERENCE: Journal of Pharmacology and Experimental Therapeutics, 1962, 136, 397-399.

DRUGS: 2 PAM (lactate or methanesulfonate) dose range 30-115 mg/kg oral
Atropine (5 mg/kg i.m.)

SUBJECTS: 52 dogs

PROCEDURES: Pre-dosed at various levels - exposed to savin - given atropine - measured survival rate

FINDINGS:
- Both oximes effective when given with atropine.

(Cont'd) 240

- "One could make the somewhat arbitrary assumption that in man, as in the dog, a blood level of oxime of at least 3 μg/ml would be needed for reasonably protective attenuation of the toxic effects of organophosphorus anticholinesterases."
- "Blood oxime level at the start of exposure appears to be a determinant of eventual death or survival...."
- "...increasing the oral dose of either 2-PAML or 2-PAMM from 30 to 75 mg/kg or even to 115 mg/kg did not have any clear effect in increasing effectiveness when the oximes were taken 2.5 or 5 hours before exposure."

COMMENT: Savin vapor (1 min)

INDEX: Oxime, Atropine, Nerve Agent, Pharmacology, Non-Human

AUTHORS: Crown, T. J., and Grove-White, I. G.

TITLE: Differential effect of atropine and hyoscine on human learning capacity

REFERENCE: British Journal of Pharmacology, 1971, 43, 464 P.

DRUGS: Hyoscine (0.4 mg), Atropine (0.6 mg), Saline (1 ml)

SUBJECTS: 12 humans

PROCEDURES: Tests (a) wordlist with immediate recall (3-30 s), (b) same as (a) with delayed recall (60-90 s), (c) number-color association test (20 min), and (d) Vigilance task [each subject received each treatment].

FINDINGS:
"Subjects receiving hyoscine showed a significant reduction in performance on both the delayed recall and the number-color association tests, but no reduction in the vigilance task, and a much smaller reduction in the immediate recall test. There was no impairment after treatment with atropine."

(Cont'd) 250

"...our results suggest hyoscine may impair the transition from short to longer term storage without impairing either short term recall or intellectual capacity as assessed by a vigilance task."

COMMENT: Hyoscine is scopolamine.

INDEX: Atropine, Drug (Other), Performance, Human

AUTHORS: Cullumbine, H., McKee, W. H. E., and Creasey, N. H.

TITLE: The effects of atropine sulphate upon healthy male subjects

REFERENCE: Quarterly Journal of Experimental Physiology, 1955, 40, 309-319.

DRUGS: Atropine sulphate (2, 3, 5 mg i.m.)

SUBJECTS: 101 humans: 44 @ 5 mg, 12 @ 3 mg, and 45 @ 2 mg

PROCEDURES: "...size of pupil, near and distant visual acuity (Snellen Test Charts), pupilary response to light and to accommodation, intraocular tension, radial pulse rate at rest, blood pressure (by auscultation over the brachial artery), electrocardiograms (3 standard leads), resting tidal volume, maximum breathing capacity, vital capacity, fasting blood sugar, glucose tolerance, blood hemoglobin concentration, total white blood cells and differential counts, rectal temperature, and the respiratory and cardiovascular response to graded loads of exercise."

(Cont'd) 260

FINDINGS:

1. "...pupils were fully dilated by all doses...no alteration in near or distant visual acuity."
2. Increased pulse rate with increasing dose.
3. "...systolic blood pressure tended to fall and the diastolic pressure to rise."
4. In some subjects there was "...sinus arrhythmia, elevation of the P wave, auricular extra-systoles, and flattened, split or inverted T waves."
5. Generally no respiratory change.
6. "After atropine, the blood sugar, blood hemoglobin and white cell counts tended to decrease."
7. Rectal temperature tended to rise then fall.
8. 'Fitness Index Pulse'- "...subjects were less fit for exercise after atropine...."
9. Repeated atropine injections --"...no clear evidence of either cumulation or tolerance to the atropine."
10. "Since the early signs of anticholinesterase poisoning are vague, and for successful treatment atropinization should be achieved before the definite, major syndrome is manifest, there should be no hesitation in administering 2 mg atropine sulphate in all cases of doubt."

INDEX: Atropine, Vision, Cardiopulmonary, Pharmacology, Human

AUTHORS: Cullumbine, H., and Miles, S.

TITLE: The effect of atropine sulphate on men exposed to warm environments

REFERENCE: Quarterly Journal of Experimental Physiology, 1956, 41, 162-179.

DRUGS: Atropine sulphate (2 mg i.m.)

SUBJECTS: 40 humans

PROCEDURES: Climatic chamber (a) hot and dry (109-112°F, 36% humidity), or (b) warm and moist (90°F, 81% humidity).
Measures - pulse rate, rectal temp, blood pressures, sweat loss, sweat chloride content, urine chloride content, urinary 17-Keto steroids, blood counts, respiration, skin temperature.

FINDINGS:
1. "In both environments acclimatization consisted of a readjustment of cardiovascular balance, an increase in sweat loss (hot and dry only), a decrease in sweat chloride content and an increase in blood volume."

(Cont'd) 270

2. "Atropine increased circulatory embarrassment by raising the pulse rate and by general vasodilation, and added to the climatic stress by limitation of sweating. In an unacclimatized or partially acclimatized individual in a hot dry environment, circulatory failure and cerebral irritation would be likely to produce casualties before failure of the heat-controlling mechanism could develop."

INDEX: Atropine, Cardiopulmonary, Cutaneous, Human

AUTHORS: Daly, W. J., Ross, J. C., and Behnke, R. H.

TITLE: The effect of changes in the pulmonary vascular bed produced by atropine pulmonary engorgement, and positive-pressure breathing on diffusing and mechanical properties of the lung

REFERENCE: Journal of Clinical Investigation, 1963, 42, 1083-1094.

DRUGS: Atropine (2 mg i.v.)

SUBJECTS: 17 humans

PROCEDURES: Measures - cardiac output, pulmonary vascular pressures, pulmonary blood volume changes. Experimental manipulations - positive-pressure breathing or pulmonary vascular engorgement produced by G-suit inflation.

FINDINGS:
"These findings suggest that atropine causes a shift of blood out of the lungs into an area where it is not effectively mobilized by G-suit inflation."

(Cont'd) 280

"In normal supine subjects, atropine increases cardiac index and decreases right arterial pressure and pulmonary artery pressure. Changes in pulmonary blood volume, estimated by an external I^{131}-counting technique, suggest that atropine causes a redistribution of the blood volume away from the lung."

COMMENT: Excellent article on pulmonary changes.

INDEX: Atropine, Cardiopulmonary, Human

AUTHORS: Dauchot, P., and Gravenstein, J. S.

TITLE: Effects of atropine on the electrocardiogram in different age groups

REFERENCE: Clinical Pharmacology and Therapeutics, 1971, 83, 274-280.

DRUGS: Atropine sulfate (1 mg/70 kg body wt., repeated at 5-min intervals)

SUBJECTS: 79 humans

PROCEDURES: Electrocardiogram tracings

FINDINGS:
- "Atropine had a significant effect on heart rate in all age groups."
- Older age groups had significantly smaller response to atropine than other age groups.
- Slowest rates occured after the first dose in adults, the second dose in children. Children had a greater decrease.
- P-R segmental shortening was common.
- T wave amplitudes increased with decreasing rate.
- A variety of arrhythmias occurred; AV dissociation most common.
- No mydriasis was reported after any dose.

(Cont'd) 290

- No CNS effects were reported in adults and older children, young children became sleepy.

COMMENT:
- Observation of EKG effects of pre-anesthetic patients.
- A larger study available is: Electrocardiography in Infants and Children by Cassels, D. F., and Ziegler, R. R., 1966.

INDEX: Atropine, Cardiopulmonary, Cortical, Human

AUTHORS: Davies, D. R., and Holland, P.

TITLE: Effects of oximes and atropine upon the development of delayed neurotoxic signs in chickens following poisoning by DFP and Sarin

REFERENCE: Biochemical Pharmacology, 1971, 21, 3145-3151.

DRUGS: P2S, Atropine, PAD, DFP, and Sarin (various doses and combinations)

SUBJECTS: Chickens (N not clearly stated)

PROCEDURES: Inject various combination of the above drugs and observe gait for signs of the delayed neurotoxicity attributed to organophosphates.

FINDINGS:
- Chickens that received 2-PAM and atropine or P2S, DFP, and atropine alone showed no neurotoxicity.
- Chickens that received DFP or sarin alone did exibit abnormal gaits following multiple sublethal doses of these drugs.

(Cont'd) 300

- P2S, PAD or atropine did not influence the development of the neurotoxicity.

INDEX: Oxime, Atropine, Musculoskeletal, Non-Human

AUTHORS: Dawson, R. M., and Bladen, M. P.

TITLE: Some adjuncts to oxime-atropine therapy for organophosphate intoxication - Their effects on acetylcholinesterase

REFERENCE: Biochemical Pharmacology, 1979, 28, 2211-2214.

DRUGS: Diazepam, Cevadine, Galanthamine

SUBJECTS: None

PROCEDURES: A purely in-vitro study by enzymatic assay, of adjuncts to standard atropine-oxime therapy.

FINDINGS:
1. Little to no inhibition of acetylcholinesterase systems.
2. No effect on the rate of reactivation or ageing of carbamylated and phosphorylated enzyme.
3. Beactyzine and chlorpromazine decreased the rate of reactivation of dimethylcarbamyl-acetylcholinesterase.
4. The effectiveness of these drugs in vivo is probably unrelated to the effects on acetylcholinesterase.

(Cont'd) 310

COMMENT: In-vitro, enzymatic system study, which seems to rule out the enzyme system.

INDEX: Atropine, Oxime, Drug (Other), Pharmacology, Non-Human

AUTHORS: DeTroyer, A., Yernault, J., and Rodenstein, D.

TITLE: Effects of vagal blockade on lung mechanics in normal man

REFERENCE: Journal of Applied Physiology, 1979, 46, 217-226.

DRUGS: Atropine 1.75 mg i.v.
Atropine Cogenor (240 mg inhalation)

SUBJECTS: 8 humans

PROCEDURES: Subjects were given atropine by i.v. route and inhalation. Measurements of respiratory airway resistance, N_2 closing volume, maximal expiratory flow volume, pressure volume, maximum flow-static recoil and esophageal elasticity were compared to non-atropinized values.

FINDINGS: "I.V. administration produced a marked decrease in lung recoil pressures and a slight increase in lung compliance, whereas inhalation did not modify the static mechanical properties of the lung."
Both routes of administration decreased respiratory airway resistance about 50%.

(Cont'd) 320

The action of nebulized particles seems to exert its effect on the large, upper airways rather than throughout the tracheobronchial tree as when given i.v.

COMMENT: Applications appear directed toward clinical medicine and airway disease. However, the study gives a good look at airway resistance issues.

INDEX: Atropine, Cardiopulmonary, Human

AUTHORS: Dirnhuber, P., and Green, D. M.

TITLE: Effectiveness of pyridostigmine in reversing neuromuscular blockage produced by soman

REFERENCE: Journal of Pharmacy and Pharmacology, 1978, 30, 419-425.

DRUGS: Pyridostigmine - (100 mg/kg i.v.)
Atropine -
(monkeys - 1 mg/kg i.v.
cats - 2 mg/kg i.v.
rabbits, rats, and guinea-pigs - 17 mg/kg i.v.)

SUBJECTS: Guinea-pigs, rats, rabbits, cats, and monkeys

PROCEDURES: The experimenters compared the recovery rate of tetanic contractions following exposure to soman in the soleus, anterior tibial and/or gastrocnemius muscle in animals pretreated, not treated, and treated following soman with pyridostigmine.

(Cont'd) 330

FINDINGS: "Pyridostigmine pretreatment produced a complete recovery of neuromuscular function following blockage by soman; the rate or recovery was similar in all species, suggesting a common mechanism of action. In the absence of pyridostigmine or if pryidostigmine was delayed until after blockage by soman, there was no recovery of neuromuscular function."

COMMENT: The paper also contains some theory as to how pyridostigmine works.

INDEX: Pyridostigmine, Atropine, Nerve Agent, Musculoskeletal, Non-Human

AUTHORS: Farag, A., Kahil, A., and Soliman, M. A.

TITLE: Comparative study of the effect of atropine, P2AM, and Buscopan

REFERENCE: Pharmacology, 1976, 14, 301-306.

DRUGS: Atropine (12-80 mg/kg), P2AM (25 mg/kg), P2AM (25 mg/kg) plus atropine (35 mg/kg), Buscopan (30-60 mg/kg), hyoscine (2-16 mg/kg) plus atropine (10-80 mg/kg), total belladonna alkaloids (12-50 mg/kg)

SUBJECTS: Rats, dogs

PROCEDURES: LD_{50}

FINDINGS:
- Atropine (alone) 70 mg/kg increases recovery significantly.
"P2AM potentiates the action of atropine giving better recovery rate...."
"Hyoscine decreases the mortality rate significantly, whereas when combined with P2AM it affects full recovery."
"Buscopan in a dose of 60 mg/kg, decreases the mortality rate significantly the same as atropine, 70 mg/kg...."

(Cont'd) 340

"Buscopan combined with P2AM increased mortality rate which may be attributed to central respiratory failure, because both drugs act peripherally."

COMMENT: Parathion poisoning.
Buscopan is hyoscine-N-butylbromide.

INDEX: Atropine, Oxime, Drug (Other), Nerve Agent, Pharmacology, Non-Human

350

AUTHORS: Firemark, H., Barlow, L. F., and Roth, L. J.

TITLE: The penetration of 2-PAM-C^{14} into brain and the effect of cholinesterase inhibitors on its transport

REFERENCE: Journal of Pharmacology and Experimental Therapeutics, 1964, 145, 252-265.

DRUGS: 2-PAM

SUBJECTS: Rats

PROCEDURES: Radioactively labeled 2-PAM was injected into controls and rats previously injected with dipterex, physostigmine, neostigmine or pentylenetrazole, and the brains measured for levels of 2-PAM.

FINDINGS: Dipterex increased concentration of 2-PAM-C^{14} in four of the eight brain regions analyzed/other cholinesterase inhibitors, hypercapnia and convulsions did not produce a similar increase. 2-PAM is actively transported by brain in vitro and dipterex inhibits this transport. It has been proposed that 2-PAM may be transported out of brain in vivo.

INDEX: Oxime, Drug (Other), Pharmacology, Non-Human

360

AUTHORS: French, M. C., Wetherell, J. R., and White, P. D. T.

TITLE: The reversal by pyridostigmine of neuromuscular block produced by soman

REFERENCE: Journal of Pharmacy and Pharmacology, 1979, 31, 290-294.

DRUGS: Pyridostigmine

SUBJECTS: Isolated rat phrenic nerve diaphragm preparations

PROCEDURES: Measurement of tetanic tension and functional AChE activity following pretreatment of the diaphragm to pyridostigmine.

FINDINGS: "Pretreatment with pyridostigmine before exposure of the diaphragm to soman, followed by removal of the anticholinesterase from organ bath, produced a return of tetanic tension and an increase of 5% in functional AChE activity...The changes in synaptic AChE activity were verified pharmacologically by showing a decrease in the blocking activity of acetylcholine in preparations pretreated with pyridostigmine in comparison to those given soman alone following removal of the anticholinesterase."

(Cont'd) 360

COMMENT: Demonstrated that pyridostigmine and soman seem to bind at a similar site on the AChE molecule.

INDEX: Pyridostigmine, Nerve Agent, Musculoskeletal, Non-Human

370

AUTHORS: Gibinski, K., Giec, L., Zmedzinski, J., Dosiak, J., and Waclawcyzk, J.

TITLE: Transcutaneous inhibition of sweat gland function by atropine

REFERENCE: Journal of Applied Physiology, 1973, 34, 850-852.

DRUGS: Atropine sulphate (0.1, 0.5, 1.0 mg)

SUBJECTS: Humans

PROCEDURES: Atropine applied electrophoretically through skin patch, measured sweating (volume and ion concentration).

FINDINGS: "Sweating was reduced by half in the treated area, ..." "The sodium and potassium concentrations of treated and blank did not differ. Apparently only the permeability of the glandular wall for the fluid is under cholinergic control." "The atropine effect on sweating is peripheral rather than mediated through the central nervous system."

"These observations suggest that only the fluid passage through the glandular wall is controlled by atropine but not the mechanism responsible for sweat electrolyte content."

INDEX: Atropine, Cutaneous, Human

380

AUTHORS: Gooding, J. M., and Holcomb, M. C.

TITLE: Transient blindness following intravenous administration of atropine

REFERENCE: Anesthesia and Analgesia, 1977, 56, 872-873.

DRUGS: Atropine (0.8 mg i.v.)

SUBJECTS: 1 human (case report)

PROCEDURES: Atropine given during transurethral resection of the prostatic gland under spinal anesthesia.

FINDINGS: Following 0.8 mg atropine i.v. --- "Approximately 5 minutes later, the patient complained of blurred vision but he could still perceive light. Pupils were widely dilated. At this time, it was felt he had developed mydriasis and cycloplegia secondary to the atropine injection. After another 5 minutes, the patient was no longer able to perceive visual stimuli." "Four hours after the onset of blindness, the patient was still unable to see. Following the installation of 3 drops of 2.5 percent pilocarpine in each eye, vision was gradually restored to previous levels."

INDEX: Atropine, Vision, Human

AUTHORS: Goto, H., Whitman, R. A., and Arakawa, K.

TITLE: Pulmonary mechanics in man after administration of atropine and neostigmine

REFERENCE: Anesthesiology, 1978, 49, 91-94.

DRUGS: (a) atropine 0.008 mg/kg i.v., (b) atropine 0.00375 mg/kg plus neostigmine 0.015 mg/kg and d-tubocurarine 1 mg, and (c) d-tubocurarine 1 mg

SUBJECTS: 6 humans

PROCEDURES: (1) total lung capacity, (2) total airway resistance, (3) forced vital capacity, (4) maximum mid-expiratory flow, and (5) maximum expiratory flow.

FINDINGS: "Total lung capacity, forced vital capacity, and peak expiratory flow rate did not change significantly after the injection of atropine. One-second forced expiratory volume percent, maximum mid-expiratory flow, and maximum expiratory flow at 50 percent of

(Cont'd) 390

total lung capacity, however, were significantly increased 10 and 60 min after the injection. The ratio of closing capacity to total lung capacity was not changed appreciably."

INDEX: Atropine, Drug (Other), Cardiopulmonary, Human

AUTHORS: Grob, D., and Johns, R. J.

TITLE: Treatment of anticholinesterase intoxication with oximes: Use in normal subjects and in patients with myasthenia gravis

REFERENCE: Journal of the American Medical Association, 1958, 166, 1855-1858.

DRUGS: 2-PAM or DAM (0.05 - 0.5 mg intra-arterial) [500-2000 mg i.v.]

SUBJECTS: Humans (N not given)

PROCEDURES: Measures
1. Muscle movement - action potentials and gross grip strength or muscle contraction.
2. Plasma and red blood cell cholinesterase activity.

Procedure - 1st anticholinesterase compound given then an attempt to reverse the resulting muscle weakness by 2-PAM or DAM.

(Cont'd) 400

FINDINGS:
- "Both 2-PAM and DAM were equally effective."
- Side effects

DAM @ 60-300 mg/min i.v. - burning sensation, moderate giddiness, drowsiness, sensation of warmth and tingling in abdomen and chest, slight reduction blood pressure, increase in heart rate.

"Administer atropine in severe intoxication, particularly by organophosphorus compounds, 2 to 4 mg intravenously, followed by 2 mg every three to eight minutes until muscarine-like symptoms disappear and whenever they reappear; a total of 24 to 48 mg may be required the first day. In less severe intoxication, give 2 mg intravenously or intramuscularly, repeat at 20-minute intervals until muscarine-like symptoms are relieved; maintain a mild degree of atropinization for 24 to 48 hours. For oxime administration in severe intoxication, give 2000 mg of 2-PAM (500 mg per minute) or DAM (200 mg per minute) intravenously; repeat dose if weakness is not relieved, or recurs. In moderate intoxication, give 1000 mg intravenously and repeat if weakness is not relieved or recurs. Alleviate convulsions if these interfere with respiration with trimethadione (Tridione), 1 Gm. intravenously every 15 minutes up to a maximum of 5 Gm., or with sodium thiopental (2.5% solution) intravenously."

COMMENT: -DAM = diacetyl monoxime.
-Used pyridostigmine as an anticholinesterase compound.

INDEX: Oxime, Pyridostigmine, Musculoskeletal, Pharmacology, Human

410

AUTHORS: Grob, D., and Johns, R. J.

TITLE: Use of oximes in the treatment of intoxication by anticholinesterase compounds in normal subjects

REFERENCE: The American Journal of Medicine, 1958, 24, 497-511.

DRUGS: 2-PAM and DAM (Comment 3)

SUBJECTS: See comments (1), (2), and (3).

PROCEDURES: Effects of anticholinesterase compounds on muscle function and the inhibition of these compounds by the oximes 2-PAM and DAM.

FINDINGS:
1. Pyridine-2-aldoxime (2-PAM) and diacetyl monoxime (DAM) reverse cholinesterase inhibition and neuromuscular block in man due to organophosphorous quatenary ammonium compounds.
2. The reversal of anticholinesterase neuromuscular block is due to both protection and reactivation of cholinesterase.

(Cont'd) 410

3. The inhibition of cholinesterase by organophosphate compounds has been considered to occur by direct phosphorylation of some group at the active center of the enzyme. Reversal of this inhibition by oximes is thought to be due to the displacement of the enzymatic group from the phosphor atom.
4. In moderate intoxication, 1000 mg of 2-PAM (500 mg/min) or DAM (200 mg/min) should be administered i.v. In severe intoxication, 2000 mg at the same rates is recommended. DAM must be administered more slowly due to increased local and systemic symptoms especially reduced blood pressure. These doses do not alleviate muscarinic effects (nausea, vomiting, abdominal cramps, diarrhea, sweating, increased salivation, increased bronchial secretion, and bradycardia).
5. 2-PAM and DAM were equally effective in reversing anticholinesterase neuromuscular block in man.

COMMENT:
(1) Primarily a review of the authors past publications in the field.
(2) Some results were discussed without including all details.
(3) Too many studies were considered to give dosage information.

INDEX: Oxime, Musculoskeletal, Pharmacology, Human

420

AUTHORS: Hardy, T. K., and Wakely, D.

TITLE: The amnesic properties of hyoscine and atropine in pre-anaesthetic medication

REFERENCE: Anaesthesia, 1962, 17, 331-336.

DRUGS: Atropine (0.6 mg), Hyoscine (0.4 mg) - based on weight of 10 stone with some adjustment for greater or lesser weights. (Morphine given to all patients.)

SUBJECTS: 200 humans

PROCEDURES: Patients were shown a line drawing just prior to anaesthesia then recalled it post-operatively (6-12 h after operation).

FINDINGS: 7/100 patients with hyoscine failed to recall picture. All patients with atropine correctly recalled picture. "Although hyoscine was found to possess amnesic properties significantly greater than atropine, the results failed to justify the marked reputation at present enjoyed by hyoscine for the production of amnesia."

(Cont'd) 420

"The fact that atropine showed less central depression than hyoscine may perhaps be explained by the fact that Meyers and Abren found equal degrees of depression only when the dose ratio of hyoscine to atropine was 1:8.6. Possibly the dose of atropine used in clinical practice may be too low to produce the same amnesic effect as clinical doses of hyoscine."

COMMENT: Brief history of both hyoscine and atropine.

INDEX: Atropine, Drug (Other), Performance, Human

430

AUTHORS: Hartley, L. H., Vogel, J. A., and Cruz, J. C.

TITLE: Reduction of maximal exercise heart rate at altitude and its reversal with atropine

REFERENCE: Journal of Applied Physiology, 1974, 36, 362-365.

DRUGS: Atropine sulfate (1 mg i.v.)

SUBJECTS: 5 humans

PROCEDURES:

Exercise - bicycle ergometer
Measured - oxygen uptake, volume, O_2 and CO_2 fractions, and heart rate
Conditions - sea level, 4,600 m altitude

FINDINGS:

- Several studies have shown that atropine does not affect maximum heart rate (under heavy exercise) at sea level — this is due to exercise reduced withdrawal of parasympathetic tone with an increase in sympathetic activity.

(Cont'd) 430

- "A mean reduction in maximal heart rate of 24 beats/min occurred at altitude which was associated with a 26% decrease in maximal O_2...Intravenous atropine increased the maximal heart rate of all subjects, and the group changed by a mean of 11 beats/min ($p<0.05$)."
- "...these results support the hypothesis that parasympathetic nervous activity contributes to the reduction in maximal exercise heart rate which occurs at altitude."
- "Hence the conclusion is inescapable that parasympathetic activity during maximal work at altitude is greater than it is at sea level (since there is none at sea level)."

INDEX: Atropine, Cardiopulmonary, Human

440

AUTHORS: Headley, D.

TITLE: Effects of atropine sulfate and pralidoxime chloride on visual, physiological, performance, subjective and cognitive variables in man: A review

REFERENCE: Military Medicine, 1982, 147, 122-132.

DRUGS: Atropine and 2-PAM

SUBJECTS: Humans

PROCEDURES: Review

FINDINGS: **ATROPINE**

Visual

1. Mydriasis and cycloplegia occurred.
2. Near point conversion was increased.
3. Dark adaptation (threshold and course) was unaltered.
4. Depth perception showed no significant change.

Pharmacological

5. Maximal blood concentration of atropine correlated well with maximum heart rate.
6. Serum half-life of atropine is estimated to be 2.5 to 3.5 h.

Physiological

7. Bradycardia commenced 2 min post i.m. injection and heart rate reached its lowest value (5 bpm decrease below baseline) at 6 min post injection. Tachycardia commenced 15 min post injection and continued until 60 min post injection.
8. Systolic blood pressure decreased.
9. Resting and working sweat gland activity decreased.
10. Rectal temperature increased above baseline within 15 min followed by a decrease below baseline by 60 min. Skin temperature at rest also increased.

Cognitive

11. Visual stimulus reaction time (RT) increased, however, there was no significant increase in auditory stimulus RT. Choice RT decreased.
12. Decrements in digital recall continued up to 60 min post injection but were not measured 75 to 120 min post i.m. injection. Subtraction by 7's showed no performance decrement.

Subjective

13. Subjective complaints include photophobia, blurred vision, headache, dry mouth, difficult micturation, lassitude, fatigue, drowziness, dizziness, lightheadedness, abdominal pain and nausea.

Performance

14. There was a significant decrement in performance during a 115-min forced march, in digging, and in some communications tasks.

15. There was no significant decrement in performance during a mock battle, running an obstacle course, or in rifle firing accuracy.
16. One hundred yard dash time was unaffected at 2 mg i.m. but increased by 1.19 s at 5 mg.

2-PAM

Physiological

17. Heart rate, blood pressure, and sweat gland output were unchanged at rest or with exercise.

Side effects

18. Side effects included a hot feeling in the facial area, a cold feeling in the nasopharyngeal area, impaired concentration, headache, dizziness, and diarrhea.

COMBINATION OF ATROPINE AND 2-PAM

19. Atropine effects were delayed.
20. Greatest effects on heart rate, blood pressure and skin temperature occur when atropine and 2-PAM are administered in the same injector.

COMMENT: A review. Many details of original investigations not included.

INDEX: Atropine, Oxime, Nerve Agent, Auditory, Vision, Cardiopulmonary, Performance, Review, Pharmacology, Human

450

AUTHORS: Holland, P., and Parkes, D. C.

TITLE: Plasma concentrations of the oxime pralidoxime mesylate (P2S) after repeated oral and intramuscular administration

REFERENCE: British Journal of Industrial Medicine, 1976, 33, 43-41.

DRUGS: P2S (500 mg i.m.)

SUBJECTS: Humans

PROCEDURES:
(1) Subjects given 500 mg P2S i.m.
(2) Subjects given (1) plus oral P2S prophylactic regimen.

FINDINGS:
Trial (1) produced no side effects.
Sixty percent of subjects in trial (2) complained of visual side effects, heaviness of eyes, blurred vision, and difficulty in accommodation after sudden head movement.

INDEX: Oxime, Pharmacology, Vision, Human

460

AUTHORS: Holland, P., Parkes, D., and Shakespeare, J.

TITLE: Concentrations of the oxime 2-hydroxyiminomethyl pyridinium methyl methane sulphonate (P2S) after intramuscular injection in humans

REFERENCE: British Journal of Pharmacology, 1972, 44, 368.

DRUGS: P2S (200, 500, 750 mg)

SUBJECTS: 55 humans (Part A), 52 (Part B), 22 (Part C)

PROCEDURES:
Exp A - P2S (200, 500, 750 mg i.m.), 55 Ss, blood @ 10, 20, 30, 60 min.
Exp B - Same as A plus blood @ 3 and 6 h, 52 Ss, all Ss predosed with 4g oral
Exp C - 22 Ss predosed orally with four 4 g doses @ 6 h intervals, then given i.m. 3 injections of 500 mg @ 20 min intervals, blood drawn at above intervals.

FINDINGS: "...intramuscular dose of 500 mg P2S or greater produced plasma P2S concentrations of 4.0 μg/ml within 5 minutes."

(Cont'd) 460

- Side effects - "No untoward discomfort was experienced by the volunteers at the 500 mg dose level, but at 750 mg a dull ache at the injection site persisted for five to six hours. Visual disturbances presenting as transient episodes of blurred vision and lasting from minutes to 1 to 2 h were experienced by fifteen of the twenty-two volunteers receiving three P2S injections. These occurred occasionally after the second injection but mainly after the third injection."

INDEX: Oxime, Pharmacology, Vision, Human

470

AUTHORS: Holland, P., Parkes, D. C., and White, R. G.

TITLE: Pralidoxime mesylate absorption and heart rate response to atropine sulphate following intramuscular administration of solution mixtures

REFERENCE: British Journal of Clinical Pharmacology, 1975, 2, 333-338.

DRUGS: Atropine (2 mg) combined with 2-PAM (either 500 mg or 750 mg) i.m. administration

SUBJECTS: 44 humans

PROCEDURES: Heart rate monitoring

FINDINGS: "This study indicates that this oxime combined with atropine sulphate can be administered IM to human subjects without significant effect on the absorption characteristics of either drug." There was some tendency for atropine to induce its initial slowing of heart rate more rapidly when combined with 2-PAM.

INDEX: Atropine, Oxime, Cardiopulmonary, Human

480

AUTHORS: Irmis, F.

TITLE: Correlation between spontaneous behaviour and cortical or hippocampal EEG in rats: Dissociation after atropine and lack of dissociation after physostigmine

REFERENCE: Activitas Nervosa Superior, 1974, 16, 48-50.

DRUGS: Atropine (16 or 25 mg/kg i.p.), Physostigmine (0.3 or 1 mg/kg i.p.)

SUBJECTS: 6 rats

PROCEDURES: EEG and general movement activity

FINDINGS:
- Physostigmine did not produce a dissociation between EEG and spontaneous behavior.
- Both doses of atropine did result in a dissociation lasting more than 40 min.
- "...hippocampal arousal ("theta") in rats does not seem to operate directly upon a cholinergic mechanism...."

INDEX: Atropine, Drug (Other), Cortical, Non-Human

490

AUTHORS: Kalser, S. C., Evans, D., Forbes, E., Kelly, M., Kelvington, E., Kanig, R., and Randolph, M.

TITLE: Decreased atropine toxicity in rats chronically exposed to cold

REFERENCE: Toxicology and Applied Pharmacology, 1967, 11, 511-522.

DRUGS: Atropine 2 ml/kg (100 μg/kg) either i.p. or i.v.

SUBJECTS: Rats (N varied)

PROCEDURES: LD 50. Also absorption studies. (Ss decapitated at 5, 20, 60, 120 s after injection or blood samples from 5-120 min after injection)
Group 1 - chronic cold - 5° for 7 weeks
Group 2 - acute cold - 5° for 24 h

FINDINGS: "Environmental conditioning to cold has been shown to alter the toxicity of atropine sulfate in rats when it is administered by an intraperitoneal, but not by an intravenous route. Rats exposed to 5°C for 49 days tolerate twice the amount of atropine sulfate tolerated by rats exposed to 5° for only 1 day. This tolerance

(Cont'd) 490

parallels the slower absorption of the drug from the peritoneal cavity compared with the absorption rates for acutely cold-exposed rats, or rats maintained at 25°. Although excretion of drug into the urine and bile is not higher for the chronic cold animal, its tissue concentrations are somewhat lower. This suggests that the cold-acclimated rat decreases the toxicity of atropine by limiting absorption rather than by increasing excretion."

"...equal toxicity to all groups when it is administered intravenously rather than intraperitoneally."

INDEX: Atropine, Pharmacology, Non-Human

500

AUTHORS: Kalser, S. C., and McLain, P. L.

TITLE: Atropine metabolism in man

REFERENCE: Clinical Pharmacology and Therapeutics, 1970, 11, 214-227.

DRUGS: Atropine (2 mg i.m.)

SUBJECTS: 4 humans (5 trials)

PROCEDURES: Analysis of blood and urine samples and expired air.

FINDINGS:

"Administration of two ^{14}C-tropine-labeled atropines to man shows the urinary excretion of 77 to 93 per cent of the injected dose in 24 hours."

"Atropine disappears very rapidly from the blood. Urinary excretion over the first 24 hours occurs at two rates; a fast rate occurring first with t1/2 of about 2 hours and a slow rate with a t1/2 of about 13 to 38 hours."

"Perhaps as much as 5 to 10 per cent of the injected dose may ultimately be committed to this route [expired air]."

(Cont'd) 500

"An effective reabsorption from the gut prevents atropine or its metabolic products from being excreted in the feces."

INDEX: Atropine, Pharmacology, Human

510

AUTHORS: Katz, B., and Miledi, R.

TITLE: The effect of atropine on acetylcholine action of the neuromuscular junction

REFERENCE: Proceedings of the Royal Society of London, 1973, 184, 221-226.

DRUGS: Atropine sulphate (10^{-4} µg/ml [approx 0.15 m M] and in some cases neostigmine methylsulphate (10^{-6} µg/ml)

SUBJECTS: Frogs - sartorius muscle (N varied - several experiments)

PROCEDURES: Intra- and extra-cellular recording

FINDINGS: "These results show that there is an important difference between the actions of atropine and curare at the neuromuscular junction. The effect of curare can be explained most simply by reversible blockage in all-or-none fashion of individual receptor molecules, leaving the free molecules to react with ACh in the normal way. Atropine, on the other hand, does not appear to block the access of ACh to receptor molecules, but reduces the elementary voltage change and shortens the molecular 'grating action'."

COMMENT: Classic article by Nobel prize winner.

INDEX: Atropine, Pharmacology, Non-Human

520

AUTHORS: Kradjan, W., Lakshminarayan, S., Hayden, P., Larson, S., and Marini, J.

TITLE: Serum atropine concentrations after inhalation of atropine sulfate

REFERENCE: American Review of Respiratory Disease, 1981, 123, 471-472.

DRUGS: Atropine (0.05 mg/kg aerosol inhalation)

SUBJECTS: 6 humans

PROCEDURES: Six male subjects with acute bronchitis were given a single aerosol dose of atropine sulfate. Spirometry and venous blood samples were obtained at 0.25, 0.5, 1.0, 1.5, 2.0 and 4.0 h after inhalation.

FINDINGS:
1. A satisfactory bronchodilator response was achieved in all subjects with maximum FEV_1 increasing 50% above observed baseline. Time of maximal improvement in FEV_1 ranged from 0.25 h to 1.5 h. Onset of effect was seen in all subjects within 0.25 h.
2. Specific airway conductance increased in all subjects when compared to the initial value.

(Cont'd) 520

3. Atropine was detected in the serum of all subjects within 15 to 30 min after drug administration, with peak concentrations 0.9 ng/ml up to 21.0 ng/ml. All subjects had dry mouth for as long as 2 h. The one subject with 21.0 ng/ml serum concentration, experienced dry mouth, disabling blurred vision, tachycardia and a "wobbly feeling".
4. There does not appear to be a correlation between peak drug concentration and absolute amount of drug administered.

COMMENT: Some tabular data did not appear to be in agreement with statements.

INDEX: Atropine, Cardiopulmonary, Vision, Spatial, Human

530

AUTHORS: Lange, P., Tiefenbach, B., and Wiezorek, W. D.

TITLE: Effect of dithiocarb on acute toxicity and acetylcholinesterase inhibition by different organophosphates in mice

REFERENCE: Proceedings of the European Society of Toxicology, 1977, 18, 284-285.

DRUGS: Antidote drug - dithiocarb (diethyldithiocarbamate) 250, 100, or 50 mg/kg
Agonists - organophosphates (a) parathion-methyl, (b) trichlorphone, and (c) dimethoate

SUBJECTS: 69 mice

PROCEDURES: LD_{50} survival times after supralethal doses

FINDINGS:
1. Significant increases in survival times when exposed to parathion-methyl if pretreated (30 min) with 250, or 200, or 50 mg/kg dithiocarb.
2. Simultaneous dosing did not result in protective action.

(Cont'd) 530

3. "At a dose of trichlorphone, 700 mg/kg, given orally all animals (control) died with a mean survival time of 18 minutes while in the group of dithiocarb pretreated animals only two mice died after one hour."
4. Pretreatment with dithiocarb did not alter lethality or survival time after dimethoate.
5. "...dithiocarb in vivo decreases the degree of inhibition of brain AChE produced by the organophosphates."

INDEX: Drug (Other), Nerve Agent, Pharmacology, Non-Human

540

AUTHORS: Light, R. W., and George, R. B.

TITLE: Oral atropine in the treatment of chronic asthma

REFERENCE: Annals of Allergy, 1977, 38, 58-61.

DRUGS: Atropine Sulfate (0.5 mg p.o.)

SUBJECTS: 6 humans

PROCEDURES: Oral atropine or placebo given to subjects for four 2-week periods. Spirograms done weekly before, 60 min after atropine, and 5 min after inhaled isoproteranol.

FINDINGS: Oral atropine did not result in improvement in brochoconstriction in low doses.

INDEX: Atropine, Cardiopulmonary, Human

AUTHORS: Linnoila, M.

TITLE: Drug effects on psychomotor skills related to driving: Interaction of atropine, glycopyrrhonium and alcohol

REFERENCE: European Journal of Clinical Pharmacology, 1973, 6, 107-112.

DRUGS: Atropine (0.5 mg), alcohol (0.5 g/kg), glycopyrrhonium (1 mg) oral administration

SUBJECTS: 170 humans

PROCEDURES: A choice reaction test, two coordination tests, and attention test.

FINDINGS: "Both atropine and glycopyrrhonium shortened reaction time and either left co-ordination unaffected or slightly improved. Anticholinergics or alcohol alone impaired attention. The combination of anticholinergics and alcohol further impaired attention whilst leaving reaction times and co-ordination unaffected."

(Cont'd) 550

"In conclusion, anticholinergics had a relaxing effect on the subjects, whilst simultaneously impairing their attention to a degree that could be considered dangerous for driving."

INDEX: Atropine, Drug (Other), Performance, Human

AUTHORS: Lipp, J., and Dola, T.

TITLE: Comparison of the efficacy of HS-6 verses HI-6 when combined with atropine, pyridostigmine and clonazepam for soman poisoning in the monkey

REFERENCE: Archives Internationales de Pharmacodynamie, 1980, 246, 138-148.

DRUGS: HS-6 (Various doses)
HI-6

SUBJECTS: Monkeys

PROCEDURES: Monkeys were exposed to varying doses of soman and given therapy as in title. Multiple physiologic parameters were monitored.

FINDINGS: The results of this study demonstrate the effectiveness of both combinations in reversing the toxic effects of soman when administered at doses as high as 60 mg/kg which is equivalent to about 10 LD_{50}'s. There did not appear to be any significant difference in the therapeutic effectiveness between the two oximes--the only difference appeared to be in the severity of the side effects. Both combinations completely suppressed the seizure activity and convulsions, and re-

(Cont'd) 560

versed the respiratory depression. The animals that received the combination containing HI-6 at a dose of 30 mg/kg exhibited severe hypotension and took longer to recover than those receiving 15 mg/kg. Of the two monkeys which received 15 mg/kg of HS-6, one died and the other had a long period of hypotension. HI-6 given at 15 mg/kg caused less severe side effects.

INDEX: Oxime, Atropine, Pyridostigmine, Nerve Agent, Cardiopulmonary, Pharmacology, Non-Human

AUTHORS: Lipp, J. A., and Dola, T. J.

TITLE: Effect of atropine upon the cerebrovascular system during soman-induced respiratory depression

REFERENCE: Archives Internationales de Pharmacodynamie, 1978, 235, 211-218.

DRUGS: Soman 20-25 mg/kg i.m.
Atropine 3 mg/kg i.v.

SUBJECTS: 5 monkeys

PROCEDURES: After methoxyflurane anesthesia, subjects given soman i.m. When severe dyspnea or apnea occurred, atropine was given. Cerebral blood flow was measured and EEG monitored.

FINDINGS:
1. Soman caused cerebral dysautoregulation of blood flow.
2. The decrease in cerebral blood flow occurring as a result of the dysautoregulation could be partly responsible for the respiratory depression.

(Cont'd) 570

3. The beneficial effects of atropine on soman-induced respiratory depression are due to rapid rise in cerebral blood flow, mean arterial blood pressure, and cerebral perfusion pressure as a result of inhibition of vagal influence peripherally and not due to any central atropine effects.

COMMENT: Limited study of only 5 animals under general anesthesia obscures results in this study - is lack of central effect due to anesthesia?

INDEX: Atropine, Nerve Agent, Cardiopulmonary, Cortical, Non-Human

580

AUTHORS: Long, G., and Marsh, H. M.

TITLE: The effect on heart rate of neuromuscular blockage reversal by pyridostigmine

REFERENCE: Anaesthesia and Intensive Care, 1981, 9, 144.

DRUGS:
1. Pyridostigmine (143 mg/kg) + D-Tubocurarine
2. Atropine (18 mg/kg)
3. Neostigmine (36 mg/kg)

SUBJECTS: 40 humans

PROCEDURES: Pyridostigmine (P) without Atropine (A), P + A or neostigmine + A was used to antagonize neuromuscular blockage induced by D-Tubocurarine, and heart rate was monitored.

FINDINGS: P alone caused an average decrease in heart of 72 to 55 beats/min at 10 min after administration. P + A did not cause a significant decrease or increase in heart rate.

INDEX: Pyridostigmine, Atropine, Drug (Other), Cardiopulmonary, Human

590

AUTHORS: Longo, V. G.

TITLE: Behavioral and electroencephalographic effects of atropine and related compounds

REFERENCE: Pharmacological Reviews, 1966, 18, 965-996.

DRUGS: Atropine (various doses)

SUBJECTS: Humans and animals

FINDINGS: The author goes through a detailed description of various effects of atropine which have been reported in humans.

Doses:

.5 - 2 mg modest stimulation of the respiratory centers.

.4 - 10 mg diminution of both the power of concentration and memory.

> 2 mg drowiness, withdrawal and tendency to sleep.

> 10 mg ataxia, loss of voluntary movements.

> 10 mg hallucinations.

COMMENT: Most of paper deals with animals.

INDEX: Atropine, Cardiopulmonary, Performance, Spatial, Human, Non-Human

600

AUTHORS: Lundy, P. M.

TITLE: The ganglionic blocking properties of the cholinesterase reactivator, HS-6

REFERENCE: Canadian Journal of Physiology and Pharmacology, 1978, 56, 857-862.

DRUGS: HS-6 (30 mg/kg or 100 mg/kg i.v.)

SUBJECTS: Cats

PROCEDURES: Cats were injected with HS-6, and the pressor response of carotid artery occlusion was measured. The results of selective superior cervical ganglion injection were also noted.

FINDINGS: "HS-6 drastically reduced the blood pressure increase produced by carotid occlusion."...."HS-6 also decreased the response of two drugs known to cause a pressor effect by ganglionic stimulation, (nicotine and DMPP) but did not decrease the response to epinephrine."...."High blood levels of HS-6 cause respiratory paralysis."

COMMENT: Experiments demonstrate the ganglionic blocking effects of HS-6.

INDEX: Oxime, Cardiopulmonary, Non-Human

610

AUTHORS: Martin, H. de V.

TITLE: Atropine sulphate absorption from an intramuscular injection of a mixture of the oxime, P2S, and atropine in exercising humans

REFERENCE: British Pharmacological Society, 1973, 47, 619.

DRUGS: Atropine (2 mg) or 2-PAM (750 mg) mixed with atropine (2 mg) or 2-PAM (750 mg)

SUBJECTS: 9 humans

PROCEDURES: Measures - heart rate, rectal and epigastric skin temperature, and sweat loss while exercising on bicycle ergometer.

FINDINGS: - "No significant differences were found between the data obtained from the men following injections of either the atropine alone or the atropine/P2S mixture. Both sets of data were higher than the corresponding control values, becoming significant at 10 min post-injection for the heart rate ($p<0.02$), 32 min for skin temperature ($p<0.05$), and 60 min for rectal temperature ($p<0.01$)."
- No significant change in sweat loss.

(Cont'd) 610

- "The data for P2S alone were the same as that for the control. Its rate of absorption was not altered by mixing it with atropine."

INDEX: Atropine, Oxime, Cardiopulmonary, Human

620

AUTHORS: Medrado, V., and Stephen, C. R.

TITLE: Effect of premedication with atropine sulphate on arterial blood-gases and pH

REFERENCE: Lancet, 1966, 1, 734-735.

DRUGS: Atropine sulphate (0.5 mg i.v. and 0.25 mg i.m.)

SUBJECTS: 47 humans

PROCEDURES: Blood samples - 20 and 40 min after administration

FINDINGS:
"No significant differences were noted in the pH, $PaCO_2$, and PaO_2 before or after administration of atropine."
"...the administration of atropine before induction of anaesthesia does not have a deleterious action on acid-base balance or on the existing PaO_2 of the patient."

INDEX: Atropine, Cardiopulmonary, Human

AUTHORS: Mendel, D.

TITLE: The effect of atropine on the cochlear and brainstem evoked responses in the guinea pig

REFERENCE: Proceedings of the Physiological Society, 1977, 271, 53-54.

DRUGS: Atropine sulphate (250 µg/kg)

SUBJECTS: Guinea pigs (N not reported)

PROCEDURES: (a) Recorded cochlear and mid-brain evoked responses; (b) stimulus 2048 clicks (4 KHz range, 10 clicks/sec, at intensity of 50 or 60 dB (N.L.))

FINDINGS: "Within limits, the more intense the sound the larger the amplitude and the shorter the latency of each wave....The results of injecting atropine depend on the initial values. When these are small and early, the waves double in amplitude as if the sound were some 30 or 50 dB louder. The latency increases by up to 0.3 ms as if the sound were some 30 or 40 dB quieter. When the responses are initially large and late, atropine has little effect."

(Cont'd) 630

COMMENT: Acetylcholine - inhibitory efferent transmitter to ear.

INDEX: Atropine, Auditory, Cortical, Non-Human

AUTHORS: Mirakhur, R.

TITLE: Comparative study of the effects of oral and IM atropine and hyoscine in volunteers

REFERENCE: British Journal of Anaesthesia, 1978, 50, 591-597.

DRUGS: Atropine (0.5, 1.0, 2.0 mg p.o. and 0.5, 1.0, 2.0 mg i.m.) Hyoscine (0.25, 0.50, 1.00 mg p.o. and 0.25, 0.50, 1.00 mg i.m.)

SUBJECTS: 6 humans

PROCEDURES: Salivary secretions, heart rate, pupilary dilation, blood pressure, and oral temperature. Subjective complaints.

FINDINGS:
1. All three i.m. doses of atropine produced a dose-related decrease in salivary secretion, which was maximal at 1 h. Maximal, dose-related decrease occurred with oral atropine at 2 h.
2. Heart rate increased after a slight initial bradycardia. Atropine 0.5 mg administered by either route caused a decrease in heart rate that was not significant. Maximum decrease occurred 1 h after i.m. injection and 2 h after oral administration.

(Cont'd) 640

3. The decrease in the number of active sweat glands was maximal at 1 h and returned gradually to baseline near 4-5 h and appeared dose related. The effects of oral administration were less pronounced and less consistent than i.m. injection although they followed the same pattern.
4. Pupillary dilatation was observed from 3 hrs onward with 0.5 and 1.0 mg i.m. and from 2 h onward with 2.0 mg i.m. atropine. Only 2.0 mg p.o. atropine produced appreciable pupil dilatation.
5. The most common subjective complaint was dry mouth and the second was drowsiness, which was dose-related.
6. The effects of i.m. and p.o. administration on mean arterial pressure and oral temperature were minimal although statistically significant.
7. The oral to i.m. ratio for atropine was 2:1 judged by the effects on salivary secretion and heart rate.

COMMENT: Only details of atropine effects are considered here. Identical data for hyoscine (scopolomine) are available in the article.

INDEX: Atropine, Nerve Agent, Drug (Other), Cardiopulmonary, Cutaneous, Vision, Human

AUTHORS: Mirakhur, R. K., Briggs, L. P., Clarke, R. S. J., Dundee, J. W., and Johnston, H. M. L.

TITLE: Comparison of atropine and glycopyrrolate in a mixture with pyridostigmine for the antagonism of neuromuscular block

REFERENCE: British Journal of Anaesthesia, 1981, 53, 1315-1319.

DRUGS: Atropine (20 μg/kg) or glycopyrrolate (10 μg/kg) with pyridostigmine (250 μg/kg)

SUBJECTS: 100 humans (50 with atropine + pyrido..., 50 with glycopyrrolate + pyrido...)

PROCEDURES: Time to reverse neuromuscular block.
Heart rate and blood pressure monitored.

FINDINGS:
"-The present study demonstrated certain advantages in the use of glycopyrrolate, when compared with atropine,...."
"-The frequency of arrhythmia was slightly greater in the group receiving atropine."
-No change in arterial pressure.

(Cont'd) 650

"-Oropharyngeal secretions were controlled better, both qualitatively and quantitatively, with glycopyrrolate."

INDEX: Atropine, Pyridostigmine, Drug-other, Cardiopulmonary, Human

AUTHORS: Moore, J., and Dundee, J. W.

TITLE: Alterations in response to somatic pain associated with anaesthesia. XII. Further studies with atropine

REFERENCE: British Journal of Anaesthesia, 1962, 34, 712-716.

DRUGS: Atropine (Ø.6 mg i.m.)

SUBJECTS: Several groups all females (see article for N's)

PROCEDURES: Analgesimetry at 2Ø, 4Ø, 6Ø, 9Ø min after injection

FINDINGS:

-"The intramuscular injection of atropine Ø.6 mg is followed by a slight, but significant, increase in sensitivity to somatic pain which can be detected 2Ø min after administration, but which has passed off within a further 2Ø min. It also decreases the analgesic action of pethidine and pethidine-phenothiazine mixtures in a similar time relationship."

(Cont'd) 660

-"It would therefore seem advisable to ensure that its preoperative administration is at least half an hour before the induction of anaesthesia."

INDEX: Atropine, Cutaneous, Human

AUTHORS: Moylan-Jones, R. J.

TITLE: The effect of a large dose of atropine upon the performance of routine tasks

REFERENCE: British Journal of Pharmacology, 1969, 37, 301-305.

DRUGS: Atropine (6 mg)

SUBJECTS: 23 humans

PROCEDURES: (a) marched 30 min, dug foxholes, performed special skill tests; (b) tests: number facility test, field medical/search rescue and treat test, map reading and compass bearing test, rifle shooting, changing wheel on vehicle; and (c) three days of testing, day 1-placebo, day 2-atropine, day 3-no injection.

FINDINGS: Atropine produced:
- "...falling off in alertness, efficiency and energy...."
- Mydriasis which lasted 48 hrs after injection (2 Ss not affected).
- "Rectal temperatures did not rise higher...."

(Cont'd) 670

- "Disorders of perception occurred in ten of the subjects after receiving atropine, and included frank visual and auditory hallucinations (one man), minor visual hallucinations such as seeing colored flashes of light (seven men), and two gustatory hallucinations in which the men reported that fresh water tasted salty. One man became disoriented and ataxic and was withdrawn from the second day's trial 1 hr after the third injection of atropine, but recovered without treatment 8.5 hrs later."
- Number facility test - no impairment in morning session, "...five men were unable to attempt the test at all on the second afternoon; two of these complained that the figures had left the paper and were floating in midair."
- Field medical team - clumsy, less efficient, plus medical officer displayed possible memory lapse.
- Map and compass reading test - performance down on morning test session but normal in afternoon session.
- Rifle shooting - no effect.
- Wheel changing - somewhat slower (not significant) and more clumsy.

COMMENT: Ss dressed in antigas clothing and battle equipment.

INDEX: Atropine, Performance, Vision, Auditory, Spatial, Human

AUTHORS: Murrin, K. R.

TITLE: A study of oral atropine in healthy adult subjects

REFERENCE: British Journal of Anaesthesia, 1973, 45, 475-480.

DRUGS: Atropine sulfate
(a) i.m. 7 μg/kg
(b) oral 9 Ss - 14 μg/kg, 6 Ss - 28 μg/kg, 3 Ss - 7 μg/kg

SUBJECTS: 9 humans

PROCEDURES: (1) Collection of saliva
(2) Pulse rate
(3) Blood pressure
(4) Pupillary diameter

FINDINGS:
-"...the ratio of oral to intramuscular dose of atropine producing equal peak depression of salivation is most likely to be 1.86:1, with 95% confidence limits of ±0.39."
-Blood pressure not much change.

(Cont'd) 680

-"The pupillary diameter did not vary more than 1 mm with any administration."
-Heart rate increase with high oral dose.
-"The variability of peak effect and variability in time taken to reach these peak effects did not differ significantly between oral or intramuscular administration of atropine."

INDEX: Atropine, Pharmacology, Cardiopulmonary, Vision, Human

AUTHORS: Namba, T., and Hiraki, K.

TITLE: PAM (pyridine-2-aldoxime methiodide) therapy for alkylphosphate poisoning

REFERENCE: Journal of the American Medical Association, 1958, 166, 1834-1839.

DRUGS: Humans - 2-PAM dose varied with each case and sometimes combined with atropine.
Rabbits - various doses.

SUBJECTS: 15 rabbits, 5 humans

PROCEDURES: Pharmacological - response to parathion poisoning.

FINDINGS: 5 humans with 'serious' parathion poisoning -
-1 g i.v. generally sufficient for recovery.
-"Cholinesterase activity of red blood cells is restored instantly and completely recovers; that of the serum recovers only transiently."
-"No serious side effect has been encountered."
-"...PAM exhibits no effect when intravenously administered in small doses for prophylactic purposes. This is probably due to the prompt excretion or inactivation of PAM. On the other hand, PAM adminis-

(Cont'd) 690

tered orally may be assumed to be a preventive agent against the decreasing cholinesterase activity in rabbits. In man it is expected to be more effective than in the rabbit...."
-"There are two types of cholinesterase, true or acetylcholinesterase and nonspecific pseudocholinesterase. In humans, the former is contained in the nervous tissue and red blood cells and is considered to play a role in neurohumoral transmission. The latter is contained in serum and is considered to have essentially no function in neurohumoral transmission but is related closely to liver function.... From these results, it is obvious that the main effect produced by the administration of PAM is the restoration of the activity of acetylcholinesterase and the effect on pseudocholinesterase is but secondary."

INDEX: Oxime, Atropine, Nerve Agent, Pharmacology, Human, Non-Human

AUTHORS: Oberst, F. W., Crook, J. W., and Koon, W. S.

TITLE: The effectiveness of 2-PAM and TMB-4 as adjuncts to atropine therapy in dogs exposed to sarin vapor by inhalation

REFERENCE: Journal of Pharmacology and Experimental Therapeutics, 1962, 136, 393-396.

DRUGS: 2-PAM (15-50 mg/kg i.v.)
TMB-4 (5-15 mg/kg i.v.)
Atropine sometimes combined with oximes
Atropine (4.5 mg i.m plus 0.5 mg i.v.)

SUBJECTS: Dogs (see tables in article for N's)

PROCEDURES: Survival - also time to regain footing

FINDINGS:
-"2-PAM and TMB-4 used as adjuncts to atropine are excellent therapeutic agents for revival of dogs exposed by inhalation to Sarin vapor."
-"No conclusions can be drawn as to which oxime with atropine caused the quicker recovery; both combinations of oxime and atropine produced about the same speed of action."

(Cont'd) 700

-"Atropine alone also has some value without artificial respiration, but the mixtures of atropine with either 2-PAM or TMB-4 are far superior. Resuscitation is much quicker with the atropine-oxime mixtures and the time of recovery is decreased."
-"It is of obvious importance to be able to treat casualties from poisoning by anticholinesterase compounds by chemotherapeutic means without the use of artificial respiration."
-"TMB-4 is much more soluble in isotonic saline than is 2-PAM, a property that is highly desirable when small volumes of a solution are to be injected. One disadvantage of TMB-4 is that in dogs it is about three times as toxic as 2-PAM."

COMMENT: Sarin

INDEX: Oxime, Drug (Other), Atropine, Nerve Agent, Pharmacology, Non-Human

AUTHORS: O'Leary, J. F., Kunkel, A. M., and Jones, A. H.

TITLE: Efficacy and limitations of oxime-atropine treatment of organophosphorus anticholinesterase poisoning

REFERENCE: Journal of Pharmacology and Experimental Therapeutics, 1961, 132, 50-57.

DRUGS: 2-PAM, 2-PAMCl, 2-PAML, P2S, TMB4, TMB_4Cl_2, DAM, MINA, Atropine (Various dose levels, also multiple drug combinations)

SUBJECTS: 24 rabbits, 20 dogs, 27 mice, 11 cats

PROCEDURES: LD_{50} determinations

FINDINGS:

-"This study demonstrates that a combination of mono- and bisquaternary oximes has the advantage of greater effectiveness than any single oxime studied as an atropine adjunct for treating GB over a wide dosage range. In addition, the combined oximes were more effective against GA than was the 2-PAM type alone, and hence probably are effective against a wider variety of anticholinesterases."

(Cont'd) 710

-"...the chloride salts contain larger proportions of oxime ions per unit weight than do the other salts, and for this reason constitute a more efficient oxime dosage form."

-"Factors which may underlie the superiority of mixed oxime therapy as presented in the foregoing studies remain to be elucidated. Two possibilities which suggest themselves are: (1) a more effective reactivation of inhibited cholinesterase in the body by mixed oximes as compared to single oximes, and (2) the existence of favorable autonomic factors in the case of the mixed oximes, not seen with single oximes...."

INDEX: Oxime, Atropine, Drug (Other), Pharmacology, Non-Human

AUTHORS: O'Leary, J. F., Kunkel, A. M., Murtha, E. F., and Somers, L. M.

TITLE: Sympathomimetic actions of 2-formyl-1-methylpyridinium choloride oxime (2-PAMCl)

REFERENCE: Federation Proceedings, 1962, 21, 112. (Papers presented at the 46th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, NJ, April 1962.

DRUGS: 2-PAMCl (therapeutic dosages)

SUBJECTS: Cats, dogs, rats

PROCEDURES: Heart rate and blood pressure monitoring, liver histology

FINDINGS:

-"Such observations in anesthetized cats and dogs indicate that 2-PAMCl at therapeutic dosage levels may increase myocardial contractions as well as peripheral vascular resistance."

-"...2-PAMCl inhibits monamine oxidase in homogenized rat liver by 50% or more at concentrations of 1 x 10^{-3} molar or less."

(Cont'd) 720

COMMENT: Abstract

INDEX: Oxime, Cardiopulmonary, Non-Human

730

AUTHORS: Pennington, L. J., and Schmidt, W. F.

TITLE: Belladonna alkaloids and phenobarbital combination pharmaceutical analysis I: High-Performance liquid chromatographic determinations of hyoscyamine - atropine and scopolamine

REFERENCE: Journal of Pharmaceutical Sciences, 1982, 71, 951-953.

DRUGS: Atropine, hyoscyamine and scopolamine

SUBJECTS: None

PROCEDURES: Liquid and column chromatography extraction methods

FINDINGS: Separation of belladonna alkaloids from preparations containing phenobarbital is possible by this method, and detectable in microgram quantities.

COMMENT: Purely laboratory assay information.

INDEX: Atropine, Pharmacology

740

AUTHORS: Preiss, D., and Berguson, P.

TITLE: Dose-response studies on glycopyrolate and atropine in conscious cardiac patients

REFERENCE: British Journal of Clinical Pharmacology, 1983, 16, 523-527.

DRUGS: Atropine (5, 7.5, 10, 15, 20, 40 mg/kg)
Glycopyrrolate (5, 7.5, 10, 15 mg/kg)

SUBJECTS: 84 humans

PROCEDURES: The dose heart rate response of atropine and glycopyrrolate were compared in patients with bradycardia in preparation for coronary bypass surgery.

FINDINGS:
Glycopyrrolate was twice as potent as atropine on a mg for mg basis in increasing heart rate.
Glycopyrrolate was slower in onset of action.
Glycopyrrolate had no central actions and had a more prolonged effect in drying secretions.
Glycopyrrolate occasionally produced marked and long lasting mydriasis.

(Cont'd) 740

COMMENT: Supports a similar study reported by Mirakhur et al., in 1981.

INDEX: Atropine, Drug (Other), Cardiopulmonary, Vision, Human

750

AUTHORS: Quinby, G. E.

TITLE: Further therapeutic experience with pralidoximes in organic phosphorus poisoning

REFERENCE: Journal of the American Medical Association, 1964, 187, 114-118.

DRUGS: 2-PAMCl, 2-PAMl, atropine (dosages varied by case)

SUBJECTS: 35 humans

PROCEDURES: Review of case histories.

FINDINGS:

- In almost all cases, 2-PAM significantly improved recovery and treatment of the various organophosphorus poisonings.
- 2-PAM (plus atropine) worked best in response to parathion poisoning and although effectiveness was not as much of a benefit in phosdrin poisoning.
- Side effects, "...dizziness, blurred vision, diplopia, headache, impaired accommodation, nausea, and tachycardia were all recognized by one or more of the conscious patients to whom 2-PAM chloride was given, but only one or a few occurred in any given patient.... vomiting during or just after the administration in our patients

(Cont'd) 750

complicated the vestibular side effects with a frequency far greater than appeared likely by coincidence. Slowing the rate of intravenous administration from 1 g in two minutes to 1 g in five minutes or longer seemed to decrease the nausea and other signs...."

INDEX: Oxime, Atropine, Pharmacology, Spatial, Human

760

AUTHORS: Richards, A. G.

TITLE: Malathion poisoning successfully treated with large doses of atropine

REFERENCE: Canadian Medical Association Journal, 1964, 91, 82-83.

DRUGS: Atropine 850 mg (over 7 1/2 days). 2-PAM (1 g)

SUBJECTS: 1 human

PROCEDURES: Case history - overdose treatment

FINDINGS: "A woman who was moribund after drinking malathion in an apparent suicide attempt was treated with very large intravenous doses of atropine (850 mg over a period of seven and a half days) and artificial respiration. She survived and was restored to good health. It is concluded that the prompt and continued use of generous amounts of atropine may save a patient from what at first appears to be fatal poisoning with an organic phosphorus insecticide." Large doses i.v. every 15 min needed to maintain respiratory rate.

COMMENT: Jerky rotatory nystagmus - amnesia.

INDEX: Atropine, Oxime, Pharmacology, Spatial, Human

770

AUTHORS: Rozsival, P., and Ciganek, L.

TITLE: Subjective visual functions and objective ocular symtomatology after large doses of atropine

REFERENCE: Ceskoslovenska Oftamologie, 1978, 34, 409-412.

DRUGS: Atropine (2, 4 mg)

SUBJECTS: N not available in summary

PROCEDURES: Measures - accommodation, distant vision, pupillar size in young and old groups.

FINDINGS: Entire summary - "The authors followed the influence of parenterally administered atropine in doses of 2 and 4 mg on accommodation, distant vision and pupillar size in groups of younger and older persons. They demonstrated a substantial deterioration of work ability for near in both age groups after administration of 4 mg of atropine. Distant vision was not altered substantially. Pupillar size altered in both age groups after intramuscular administration of atropine with statistical significance."

COMMENT: English language summary only.
INDEX: Atropine, Vision, Human

780

AUTHORS: Schallert, T., DeRyck, M., and Teitelbaum, P.

TITLE: Atropine stereotypy as a behavioral trap: A movement subsystem and electroencephalographic analysis

REFERENCE: Journal of Comparative and Physiological Psychology, 1980, 94, 1-24.

DRUGS: Atropine sulfate (50-75 mg/kg)

SUBJECTS: Rats

PROCEDURES: An analysis was made of the movement subsystems involved in the stereotyped behaviors and EEG activity.

FINDINGS: Instead of scanning briefly (like control rats) drugged rats would continue to engage in rapid, repetitive scanning.

INDEX: Atropine, Musculoskeletal, Cortical, Non-Human

AUTHORS: Seppala, T., and Visakorpi, R.

TITLE: Psychophysiological measurements after oral atropine in man

REFERENCE: Acta Pharmacologica et toxicologica, 1983, 52, 68-74.

DRUGS: Oral atropine sulfate (0.85 or 1.7 mg)

SUBJECTS: 8 humans

PROCEDURES: Baseline plus 1, 2, 4 h after drug. Measures (a) pupil diameter, (b) heart rate, (c) near point of vision, (d) systolic and diastolic blood pressure, (e) flicker fusion test, (f) short-term memory test, (g) choice reaction test, (h) digit symbol substitution test, (i) time anticipation reaction test, (j) hand-eye coordination, (k) pencil threading test, (l) reflex rate, (m) proprioceptive tests, (n) lateral gaze nystagmus, (o) extraocular muscle balance, (p) standing steadiness, and (q) subjective assessment.

FINDINGS:
1. Pupils dilated after 1 h.
2. Heart rate - 0.85 mg 1st decrease @ 1 h followed by slight increase - 1.7 mg produced tachycardia after 1 h.
3. Near-point of vision increased with dose.

(Cont'd) 790

4. Blood pressure unchanged.
5. Flicker recognition and short-term memory - dose related impairment.
6. Choice reaction - mixed results with no influence on accuracy.
7. Digit symbol substitution and time anticipation - no effect.
8. Increase in coordination errors.
9. Pencil threading, reflex rate, and hand proprioception - unaltered.
10. Foot proprioception impaired.
11. Produced nystagmus expecially @ 1 h.
12. No sway differences.

INDEX: Atropine, Vision, Cardiopulmonary, Performance, Spatial Human

AUTHORS: Seppala, T., and Visakorpi, R.

TITLE: Effect of atropine on shooting: A field trial

REFERENCE: Military Medicine, 1983, 148, 673-675.

DRUGS: Atropine (2 mg)

SUBJECTS: 12 males

PROCEDURES: 6 experimental and 6 controls. Field shooting trial, regular prone position (150 m).

FINDINGS:

	Placebo	Atropine	P
Pupil diameter (mm)	3.7±1.0	4.4±0.9	<0.01
Near point (cm)	9.4±2.1	11.0±1.6	<0.01

The difference between the shooting scores during placebo (mean±SD: 80.8±9.0) and during atropine (76.5±8.4) was significant according to the paired one-tailed t-test ($t=1.87$, $p<0.05$, $n=12$).

(Cont'd 800)

COMMENT: Cadets reported subjective observations:

1. Blurred vision
2. Difficulties in accommodation
3. Poor sightings

INDEX: Atropine, Performance, Vision, Human

AUTHORS: Sidell, F. R., Magness, J. S., and Bollen, T. E.

TITLE: Modification of the effects of atropine on human heart rate by pralidoxime

REFERENCE: Clinical Pharmacology and Therapeutics, 1970, 11, 68-76.

DRUGS: 2-PAM (600 mg [30%]), atropine (2 mg) -- Cond. A. atropine one arm, saline in other arm; Cond. B. 2 PAM one arm, saline in other; Cond. C. atropine one arm, 2-PAM in other; Cond. D. atropine + 2-PAM in one arm, saline in other.

SUBJECTS: 8 humans

PROCEDURES: Heart rate monitoring - 3 days between conditions. Number facility test, pupillary diameters, pain questionnaire.

FINDINGS:
1. "When the drugs were mixed before injection, the heart rate response had a significantly longer latent period than that when they were given simultaneously but separately. The addition of pralidoxime to atropine somehow impeded the action of atropine."
2. "...pralidoxime solutions did cause more pain, although the difference was not great."

(Cont'd) 810

3. "The mean NF [number facility] scores of all four groups showed a mild decrement (10 to 15 per cent) at 1.5 hrs after injection with recovery to baseline values by 3.5 hrs."
4. Pupil size, "enlargement was slight and of dubious significance".
5. Pralidoxime by itself produced no change in heart rate.

COMMENT: See note on muscle necrosis with 50% concentrations of 2-PAM.

INDEX: Oxime, Atropine, Cardiopulmonary, Performance, Vision, Human

AUTHORS: Smith, A. P., and Muir, A. W.

TITLE: Antidotal action of the oxime HS6 at the soman poisoned neuromuscular junction of the rat and guinea-pig

REFERENCE: Journal of Pharmacy and Pharmacology, 1977, 29, 762-764.

DRUGS: HS-6 (130 mg/kg i.v. X 3 doses)

SUBJECTS: Gastrocnemius muscle and sciatic nerve preparations from the rat and guinea-pig

PROCEDURES: Isometric single twitch and tetanic responses were recorded following injection of soman and later HS-6.

FINDINGS: Given 1 min after soman, HS6 restored 80-90% of the tetanic tension. Non-significant reversal was obtained if the HS-6 was delayed to 6 min. In the rate, 17% cholinesterase activity was regenerated within 10 min by HS-6 given 1 min after soman infusion, but no reactivation was detected when HS-6 administration was delayed for 64 min.

(Cont'd) 820

COMMENT: This demonstrates the rapid "aging" of the soman inhibited acetylcholinesterase.

INDEX: Oxime, Musculoskeletal, Pharmacology, Non-Human

AUTHORS: Smith, P. K., and Hemingway, A.

TITLE: Effect of some atropine-like drugs on swing sickness

REFERENCE: Proceedings of the Society for Experimental Biology and Medicine, 1946, 63, 206-208.

DRUGS: Atropine (1 mg), scopolamine (.5, .75 mg), l-hyoscyamine (1 mg), homatropine (12 mg), benzoyltropine (50 mg), demerol (100 mg), paratrine (250 mg)

SUBJECTS: Number of subjects tested varied with drug - usually 20 Ss/drug. Total atropine Ss was 126 (placebo 365). Humans.

PROCEDURES: (a) Swing test - two pole (max. 20 min or when S vomited)
(b) salivation, pulse rate, blood pressure, accommodation

FINDINGS: "In general it may be said that scopolamine, atropine, and l-hyoscyamine were effective whereas homatropine, benzoyltropine, and bonzoyloscine were of a lower order of usefulness. None of the remedies, in the doses employed, produced effects on the pulse rate,

(Cont'd) 830

blood pressure or near point of accommodation. Significant decreases in salivary flow were produced by atropine, hyoscyamine, and scopolamine."

INDEX: Atropine, Drug (Other), Spatial, Cardiopulmonary, Vision, Human

840

AUTHORS: Spruit, D., and Reynen, A. T. A.

TITLE: Pattern of sweat gland activity on the forearm after pharmacologic stimulation

REFERENCE: Acta Dermatovener (Stockholm), 1972, 52, 129-135.

DRUGS: Atropine (0.1 ml 0.001%)
Acetylcholine (0.02 ml 0.01%)

SUBJECTS: 1 human

PROCEDURES: Pattern of sweat duct activity on forearm after injections.

FINDINGS: "Following atropine injection the epicentre of activity is found to be displaced from the site of injection...."

COMMENT: More of a technique article and not pharmacologically oriented.

INDEX: Atropine, Pharmacology, Human

850

AUTHORS: Staniforth, D. H.

TITLE: The QT interval and cycle length: The influence of atropine, hyoscine, and exercise

REFERENCE: British Journal of Clinical Pharmacology, 1983, 16, 615-621.

DRUGS: Atropine (0.6, 1.2, and 1.8 mg i.v.)
Hyoscine (0.4, and 0.8 mg i.v.)

SUBJECTS: 27 humans

PROCEDURES: Healthy male subjects were given atropine or hyoscine by i.v. injection. EKG recordings were made while exercising on a bicycle ergometer. Stroke volume was also measured.

FINDINGS: "The relationship between QT and cycle length following the exercise protocol was found to be best represented by Bazett's correction."

(Cont'd) 850

COMMENT: One of several attempts to mathematically correlate QT interval and cycle length with exercise, position, and anticholinergics.

INDEX: Atropine, Drug (Other), Cardiopulmonary, Human

860

AUTHORS: Stitcher, D. L., Harris, L. W., Heyl, W. C., and Alter, S. C.

TITLE: Effects of pyridostigmine and cholinolytics on cholinesterase and acetylcholine in soman

REFERENCE: Drugs and Chemical Toxicology, 1978, 1, 335-378.

DRUGS: Pyridostimine, atropine, benactyzine, and soman

SUBJECTS: Rats (N not clearly stated)

PROCEDURES: Rats were treated with these drugs in various combinations and then acetycholine levels were measured in the cerebral tissue. Cholinesterase activity was measured in the blood and brain.

FINDINGS:
Soman reduced AChE to 15% of control in blood and brain.
Soman increased brain ACh to 137.4% of control.
Pyridostigmine reduced blood AChE to 31.6% with no effect on brain AChE.
Prophylatically pyridostigmine protected 70% of blood AChE but no brain AChE.
Benactyzine was more effective than atropine in reducing brain ACh.

A prophylaxis of pyridostigmine, atropine, and benactyzine was effective in controlling ACh in rats poisoned with soman.

COMMENT: Central protection was due to atropine and benactyzine since pyridostigmine has no central effect.

INDEX: Pyridostigmine, Atropine, Drug (Other), Nerve Agent, Pharmacology, Non-Human

870

AUTHORS: Sundwall, A.

TITLE: Plasma concentration curves of N-methylpyridinium-2-aldoxime methane sulphonate (P2S) after intravenous, intramuscular and oral administration in man

REFERENCE: Biochemical Pharmacology, 1960, 5, 225-230.

DRUGS: 2-PAM (i.m. 2Ss - 20 mg/kg, 10Ss - 30 mg/kg)
(Oral 6 Ss - 1 g)

SUBJECTS: 2 Ss i.v., 12 Ss i.m., 6 Ss oral - all humans

PROCEDURES: Plasma levels of 2-PAM

FINDINGS:

i.m. - therapeutic plasma levels (approx. 4 μg/ml) reached in approx. 5-10 min
- peak levels (approx. 15 μg/ml) in approx. 20 min.
- only 3 Ss tested beyond 90 min (120 to 180 min); all maintained a level exceeding 5 μg/ml.
- pain at site of injection (30 mg/kg) also "...sciatic neuralgia in the leg of the injected side, but these symptoms disappeared within a few hours."

Oral - slow rise
- peak levels (approx. 4-5 g/ml) after 2 to 3 h
- "...oral administration alone is of little therapeutic value as the rate of absorption is too slow."

i.v. - 2 Ss given i.v. injection (20 mg/kg)
- "...mild side reactions such as dizziness, blurred vision, and diplopia, but these symptoms vanished within a few minutes."

INDEX: Oxime, Pharmacology, Spatial, Vision, Musculoskeletal, Human

880

AUTHORS: Sundwall, A.

TITLE: Minimum concentrations of N-methylpyridinium-2-aldoxime methane sulphonate (P2S) which reverse neuromuscular block

REFERENCE: Biochemical Pharmacology, 1961, 8, 413-417.

DRUGS: P2S (From $5x10^{-6}$ to $1x10^{-3}$M) in vitro, 10 mg/kg in vivo

SUBJECTS: In vitro (rats, frogs) - In vivo (cats)

PROCEDURES: Rat phrenic nerve diaphragm preparation.

FINDINGS:
"...plasma levels of P2S above 4 μg/ml counteract neuromuscular block in vitro and in vivo, and bradycardia, hypotension and respiratory failure in vivo. Atropine was not used in the experiments and it is therefore possible that the concentrations of P2S together with atropine needed for therapeutic effect might be lower, since atropine may prolong survival, thus giving the oxime more time to reactivate the inhibited enzyme."
"If the results are valid in man, intramuscular injection of from 20 to 30 mg P2S per Kg body weight should yield therapeutic plasma concentrations after from 5 to 10 min. P2S is equally effective

against the neuromuscular block produced by sarin, 37 S-N, and 37 S-N+...but is much less effective against the block produced by tabun."

COMMENT: Organophosphorous cholinesterase inhibitors used:
1. Tabun
2. Sarin
3. 37, S-N, methylisopropoxy-(2-dimethylamino-ethylthio)-phosphine oxide acid oxalate
4. 37, $S\text{-}N^{+}$, methylisopropoxyphosphory thiocholine iodide

INDEX: Oxime, Nerve Agent, Pharmacology, Non-Human

890

AUTHORS: Tredici, T. J., and Epstein, D. L.

TITLE: Ocular complications of drug therapy

REFERENCE: Aerospace Medicine, 1972, 43, 898-902.

DRUGS: Atropine, homatropine, tropicamide, chloroquine, pilocarpine, physostigmine

SUBJECTS: Human

PROCEDURES: Review of clinical literature.

FINDINGS: Atropine will incapaciate pilot for as long as two weeks (cycloplegia). Shorter-acting anti-cholinergic drugs such as homatropine or tropicamide can be substituted. Systemic adrenergic and systemic anticholinergic medications possibly could precipitate angle-closure glaucoma. Atropine has induced this in predisposed eyes. Chloroquine may cause fine white dots in the corneal epithelium in a whorl pattern which may cause symptomatic halos and possibly photophobia. Oral contraceptive noted to cause edema of the corneal epithelium which can cause secondary changes in refraction.

INDEX: Atropine, Drug (Other), Vision, Human

AUTHORS: Van Der Meer, M. J., Hundt, H. K. L., and Muller, F. O.

TITLE: Inhibition of atropine metabolism by organophosphate pesticides

REFERENCE: Human Toxicology, 1983, 2, 637-640.

DRUGS: Atropine (0.03-0.05 mg/kg)

SUBJECTS: 8 humans

PROCEDURES: Tritiated atropine was given to organophosphate poisoned patients, urine collected at intervals and tested for atropine and metabolites using thin paper chromatography.

FINDINGS: Only atropine was detected in organophosphate poisoned patients, but five metabolites of atropine were found in the urine of normal human volunteers.
"It is concluded that acute organophosphate poisoning blocks atropine metabolism by inhibiting the hepatic microsomal enzymes."

(Cont'd) 900

COMMENT: Uppal et al. in 1982 showed that chronic low-level exposure to malathion possibly stimulated an increase in activity of hepatic microsomal enzymes.

INDEX: Atropine, Nerve Agent, Pharmacology, Human

AUTHORS: Virtanen, R., Kanto, J., Iisajo, E., Iisajo, M., and Sjovall, S.

TITLE: Pharmacokinetic studies on atropine with special reference to age

REFERENCE: Scandanavian Society of Anaesthesiology, 1982, 26, 297-300.

DRUGS: Atropine (0.010 mg/kg i.m., 0.015 mg/kg i.m. and 0.020 mg/kg i.v.) while under anesthesia

SUBJECTS: 52 humans

PROCEDURES: Patients under combination anesthesia were given a single bolus of 0.02 mg/kg i.v. atropine, and samples were drawn from contralateral antecubital vein at 0, 2, 5, 10, 15, 30, 45 and 60 min, then at 2, 3, 4, 5, 6, 12 and 24 h. Patients under local anesthesia were given 0.01 mg/kg i.v. atropine and 0.015 mg/kg i.m. atropine boluses. Samples were analyzed 8-80 min following i.v. administration and 45-105 min following i.m. administration.

(Cont'd) 910

FINDINGS:

1. Age has a clinically significant effect on atropine pharmacokinetics. In elderly subjects [over 65 y], clearance values were lower, and elimination phase half-life was significantly longer in comparison to adults.
2. Children under 2 years of age also showed prolonged elimination phase half-lives in comparison to adults.
3. Age had no effect on atropine serum protein binding.
4. Atropine was found in CSF after a single 0.015 mg/kg i.m. injection but not after a single 0.010 mg/kg i.v. injection.

INDEX: Atropine, Nerve Agent, Pharmacology, Human

920

AUTHORS: Virtanen, R., Kanto, J., and Lisalo, E.

TITLE: Radioimmunoassay for atropine and l-hyoscyamine

REFERENCE: ACTA Pharmacologica et Toxicologica, 1980, 47, 208-212.

DRUGS: Atropine (1.3 mg i.v.)

SUBJECTS: 2 humans

PROCEDURES: Two female patients were given preanesthetic atropine. Serum atropine decay curves were obtained using RIA technique.

FINDINGS: The initial rapid decay of serum atropine correlates with the rapid clinical response of the heart rate.
"Despite the high volume of distribution, it apparently has no cumulative properties due to the rather high total serum clearance value."

COMMENT: Heart rate only was used as a measure of serum clearance. No measure of minute quantities remaining in tissue was attempted.

INDEX: Atropine, Pharmacology, Cardiopulmonary, Human

930

AUTHORS: Wadia, R. S., Ichaporia, R. N., Karnik, V. M., Relwani, G. S., and Grant, K. B.

TITLE: Cholinesterase levels in diazinon poisoning and after atropine treatment

REFERENCE: Journal of the Indian Medical Association, 1972, 59, 234-238.

DRUGS: Atropine doses ranging from 1.2 mg to 24 mg (atropine only, no 2-PAM)

SUBJECTS: 17 humans with diazinon poisoning (mild or moderate)

PROCEDURES: Measured - Serum cholinesterase (pseudo ChE)
RBC cholinesterase (true ChE)

FINDINGS:
- Atropine alone was an effective treatment for mild or moderate diazinon poisoning.
- "...we suggest that the mild case should get 3 mg immediately and 2 mg every hour for the first few hours, and a moderate case should get 6 mg to start with. The severe case may be started with 9 mg."
- "At the time of admission there is poor correlation between the severity of diazinon poisoning and the level of pseudo ChE."

(Cont'd) 930

- "Pulmonary edema, usually mild in these cases, subsided in four hours."

COMMENT: Also reported in vitro experiment, which included 2-PAM.

INDEX: Atropine, Pharmacology, Human

940

AUTHORS: Wagner, G., and Levin, R. J.

TITLE: Effect of atropine and methylatropine on human vaginal blood flow, sexual arousal and climax

REFERENCE: Acta Pharmacologica et Toxicologica, 1980, 46, 321-325.

DRUGS: Atropine (0.035 mg/kg i.v.)
Methylatropine (1 mg orally)

SUBJECTS: 11 humans

PROCEDURES: Vaginal temperatures were used as a measure of blood flow at basal, sexual stimulation, and climax stages while under the influence of anticholinergic.

FINDINGS: No differences in temperature/blood flow were found between atropinization and baseline, nor was there any impairment of sexual response. Results suggest that vasodilatation in the vagina may not be governed by cholinergic nerves.

COMMENT: Poorly understood neurophysiologic basis of hemodynamics of the vagina.

INDEX: Atropine, Cardiopulmonary, Performance, Human

AUTHORS: Wetherell, A.

TITLE: Some effects of atropine on short-term memory

REFERENCE: British Journal of Clinical Pharmacology, 1980, 10, 627-628.

DRUGS: Exp 1 - 2 mg atropine sulfate in 2 ml water or 2 ml saline
Exp 2 - 2 mg atropine sulfate - oral or placebo

SUBJECTS: Exp 1 - 10 humans
Exp 2 - 6 humans

PROCEDURES: Exp 1 - digit recall task - before, 60 and 120 min after.
Exp 2 - same task 75 min after plus 'Associate Memory' subtest of Wechsler.

FINDINGS: Exp 1 - "At 60 min after dosing, atropine treated subjects recalled fewer digits than they did before treatment or when treated with placebo." No significant decrement at 120 min.
Exp 2 - No significant differences on digit recall test or 'Associate Memory' test. There were significant decrements at 120 and 180 min using 'free recall' procedure.

(Cont'd) 950

"Thus, the results suggest that atropine, like scopolamine, impairs memory function by an effect on information storage, rather than retrieval processes."

INDEX: Atropine, Performance, Human

960

AUTHORS: Wolthuis, O., Vanwersch, R. A. P., and Van Der Wiel, H. J.

TITLE: The efficacy of some bis-pyridinium oximes as antidotes to soman in isolated muscles of several species including man

REFERENCE: European Journal of Pharmacology, 1981, 70, 355-369.

DRUGS: Bis-pyridinium oximes (HI-6) - soman
- sarin

SUBJECTS: Various in vitro muscle preps from rat, guinea pig, dog, and human

PROCEDURES: Expose the muscle preparation to the toxin; test its function add antidote and retest function

FINDINGS: "The oximes tested, mostly HI-6, were quite effective as soman antidotes in rats, guinea pigs and dogs but not human preparations."
"In human preps they were effective against sarin."

INDEX: Oxime, Nerve Agent, Musculoskeletal, Human, Non-Human

970

AUTHORS: Wurzburger, R. J., Miller, R. L., Boxenbaum, H. G., and Spector, S.

TITLE: Radioimmunoassay of atropine in plasma

REFERENCE: The Journal of Pharmacology and Experimental Therapeutics, 1977, 203, 435-441.

DRUGS: Atropine (0.0833 mg/kg body weight)
Atropine analogs

SUBJECTS: 2 dogs

PROCEDURES: Atropine antibodies were prepared in rabbits with tritium tags. Plasma from dogs injected with atropine could then be measured by RIA techniques.

FINDINGS: As little as 6.25 ng of atropine could be detected in plasma by this method.

COMMENT: New development of a specific, sensitive method for detecting small amounts of circulating atropine by RIA techniques.

INDEX: Atropine, Pharmacology, Non-Human

AUTHORS: Yonkov, D., and Roussinov, K.

TITLE: Influence of atropine and methlatropine on the memory-improving effect of central stimulants

REFERENCE: Agressologie, 1981, 22, 199-204.

DRUGS: Atropine sulphate (20, 50 mg/kg i.p.), methylatropine (20, 50 mg/kg i.p.)

SUBJECTS: 600 rats

PROCEDURES: Active avoidance training (one session) followed by 'memory testing' 24 hrs and 14 days after training.

FINDINGS:
- "Atropine in doses of 2 to 50 mg/kg administered before training markedly deteriorates the indices of learning and memory. Applied in higher doses immediately after training atropine also deteriorates the indices of memory upon testing performed 24 hours later...."

(Cont'd) 980

- Does not appear to have a central sedative effect.
- "Methylatropine used in the same doses as atropine does not affect the learning and memory processes."

INDEX: Atropine, Performance, Non-Human

AUTHORS: Zarro, V. J., and Dipalma, J. R.

TITLE: The sympathomimetic effects of 2-pyridine aldoxime methylchloride (2-PAMCl)

REFERENCE: Journal of Pharmacology and Experimental Therapeutics, 1965, 147, 153-160.

DRUGS: 2-PAM (several doses - all not reported - range 10-200 mg/kg)

SUBJECTS: 52 dogs

PROCEDURES: Blood pressure, nictitating membrane movement

FINDINGS:
"2-Pyridine aldoxime methychloride has been shown to cause an increase in blood pressure when a dose of 10 mg/kg or more was administered intravenously to dogs."
"...transient spike followed by a sustained rise."
- Spike caused by ganglionic stimulation.
- Sustained rise caused either by release of catecholamines or by blocking their reuptake.
"In many of its actions, 2-PAMCl resembles nicotine."

(Cont'd) 990

COMMENT: Several surgical and pharmacological treatments were used to evaluate (isolate) target mechanisms (see article for full details).

INDEX: Oxime, Cardiopulmonary, Non-Human

AUTHORS: Zsigmono, E. K., Matsuki, A., and Sharafabadi, C.

TITLE: Atropine and cardiac arrhythmia

REFERENCE: New England Journal of Medicine, 1973, 288, 635.

DRUGS: Atropine (.6mg i.v.)

SUBJECTS: 10 humans

PROCEDURES: Administer drug and check heart rate in 30 s.

FINDINGS: .6 mg of atropine i.v. will increase heart rate 18 to 30% in 30 s.

COMMENT: Encourages titration of drug dose.

INDEX: Atropine, Cardiopulmonary, Human

SUBJECT INDEX

Atropine 10,20,30,40,50,60,80,90,100,110,120,130,140,150,160,190,200,220,230,240,250,260,270,280,290,300,310,320,330,340,370,380,390,420,430,440,470,480,490,500,510,520,540,550,560,570,580,590,610,620,630,640,650,660,670,680,690,700,710,730,740,750,760,770,780,790,800,810,830,840,850,860,890,900,910,920,930,940,950,970,980,1000

Auditory 40,440,630,670

Cardiopulmonary 20,180,190,200,220,230,260,270,280,290,320,390,430,440,470,520,540,560,570,580,590,600,610,620,640,650,680,720,740,790,810,830,850,920,940,990,1000

Cortical 290,480,570,630,780

Cutaneous 270,370,640,660

Drug (other) 20,40,110,120,130,140,150,170,190,250,310,340,350,390,420,480,530,550,580,640,650,700,710,740,830,850,860,890

Human 10,20,40,50,60,70,80,90,100,160,170,180,190,200,220,230,250,260,270,280,290,320,370,380,390,400,410,420,430,440,450,460,470,500,520,540,550,580,590,610,620,640,650,660,670,680,690,740,750,760,770,790,800,810,830,840,850,870,890,900,910,920,930,940,950,960,1000

Musculoskeletal 210,300,330,360,400,410,780,820,870,960

Nerve Agent 240,330,340,360,440,530,560,570,590,640,690,700,860,880,900,910,960

Non-Human 30,110,120,130,140,150,210,240,300,310,330,340,350,360,480,490,510,530,560,570,600,630,690,700,710,720,780,820,860,880,960,970,980,990

Oxime 30,70,150,180,210,240,300,310,340,350,400,410,440,450,460,470,560,600,610,690,700,710,720,750,760,810,820,870,880,960,990

Performance 130,250,420,440,550,590,670,790,800,810,940,950,980

Pharmacology 10,30,50,70,80,90,100,120,150,180,240,260,310,340,350,400,410,440,450,460,490,500,510,530,560,680,690,700,710,730,750,760,820,840,860,870,880,900,910,920,930,970

(Cont'd) **SUBJECT INDEX**

Pyridostigmine 330,360,400,560,580,650,860

Review 140,440

Spatial 60,110,520,590,670,750,760,790,830,870

Vision 60,160,170,260,380,440,450,460,520,640,670,680,740,
770,790,800,810,830,870,890

END